

STOELTING'S

Pharmacology &

Physiology *in*

Anesthetic Practice

SIXTH EDITION

Pamela Flood
James P. Rathmell

ASSOCIATE EDITOR
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Wolters Kluwer

Stoelting's

**Pharmacology
& Physiology in
Anesthetic Practice**

Sixth Edition

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Pharmacology & Physiology in Anesthetic Practice

Sixth Edition

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My coauthors and I dedicate this sixth edition of *Stoelting's Pharmacology & Physiology in Anesthetic Practice* to our dear colleague, coauthor, and friend, Dr. Mohamed A. Naguib, who passed away in 2020 at the age of 68 years.

Mohamed was a clinical anesthesiologist, a National Institutes of Health–funded basic scientist, and an entrepreneur who founded a company to develop new therapies for neuropathic pain based on his research. He was the mentor of record to many, including some of his coauthors in this edition. He was an unofficial mentor to countless others, including nearly the entire community of clinical pharmacologists in anesthesia.

You have likely read at least some of his more than 400 scientific papers and many books and book chapters. Mohamed's seven (!) chapters in the sixth edition of *Stoelting's Pharmacology & Physiology in Anesthetic Practice* reflect his academic rigor and clear writing. They also reflect his dedication to teaching; Mohamed was the first author to complete his chapters for this edition. His chapters in this edition reflect his academic breadth, ranging from analgesic pharmacology to neuromuscular physiology.

Those of you who were fortunate to know Mohamed will miss his enthusiasm for science, ready smile, and dry wit. I fondly recall discussing his elegant study of the mechanism that underlies anesthetic-induced cognitive dysfunction in neonatal rats. This is among my favorite papers in the anesthesiology literature. Mohamed demonstrated that the neurologic deficit in development induced by anesthesia in neonatal rats could be reversed with an enriched environment.

Sitting at a back table at a meeting on anesthetic mechanisms, Mohamed described how he created an enriched environment for a rat. How did he know what a baby rat would find entertaining? He leveraged his experience as a parent, creating a playroom for his baby rats. He placed a “play group” of six baby rats in a large space (preschool) and filled it with toys including running wheels and fun stuff for the rats to explore. Our discussion broke down into laughter about his baby rat playroom, with both of us concluding it might be more fun than the meeting we were attending. We were laughing so hard that we disrupted the speaker!

Oops . . .

That was the last time I saw Mohamed.

Mohamed's scholarship, intellectual rigor, and ability to clearly explain complex concepts are fully evident in this edition of *Stoelting's Pharmacology & Physiology in Anesthetic Practice*. We will miss this amazing clinician, scientist, teacher, and friend.

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My journey with *Pharmacology and Physiology in Anesthetic Practice* began in the early 1980s with what seemed an impossible dream, a single-author anesthesia textbook devoted to the *daily application of principles of pharmacology and physiology in the care of patients*. Many yellow tablets later (my computer skills were in their infancy); an understanding family, residents, and faculty in the Department of Anesthesia at Indiana University School of Medicine; and the unwavering support and encouragement of a special friend and publisher, the first edition of *Pharmacology and Physiology in Anesthetic Practice* appeared in the fall of 1986.

The acceptance of the textbook by students, trainees, and practitioners over the years has been incredibly rewarding to me personally and served as the stimulus to create revisions for the next three editions with Simon C. Hillier, MB, ChB, joining me as a coeditor for the fourth edition that appeared in 2006.

It is clearly time for a new edition and a new approach if *Pharmacology and Physiology in Anesthetic Practice* is going to continue to meet its original goal of *providing an in-depth but concise and current presentation of those aspects of pharmacology and physiology that are relevant either directly or indirectly to the perioperative anesthetic management of patients*.

In this regard, I could not be more pleased and honored that Drs. Pamela Flood, James P. Rathmell, and Richard D. Urman agreed to act as coeditors of this multi-authored sixth edition. Their unique expertise and access to recognized authorities in the wide and expanding areas of pharmacology and physiology that impact the perioperative care of patients is clearly evident in this edition.

On behalf of myself and all our past (and future) readers, I thank the new coeditors and their authors for keeping *Stoelting's Pharmacology & Physiology in Anesthetic Practice* current with the times and fulfilling the dream I had more than 30 years ago.

Robert K. Stoelting, MD

Robert Stoelting is among the best writers in our specialty. His signature textbook, *Pharmacology and Physiology in Anesthetic Practice*, resonated with residents and faculty, including us, because it was exceptionally well written. It has been the “go-to” reference since its first edition in 1986. Dr. Stoelting’s clear prose succinctly covered the drugs we were using in our daily practice. His explanations of physiology were intuitive and sensible. Every chapter in the earlier editions spoke with the same voice, reflecting the many years he invested in refining his single-authored textbook. Even though Dr. Hillier joined him as coauthor of the fourth edition, the text continued to resonate as a single voice.

When first approached about revising the textbook for the fifth edition, we turned down the project. It seemed impossible to reproduce the clarity of Dr. Stoelting’s work. However, the option for the publisher was to transform *Pharmacology and Physiology in Anesthetic Practice* into a conventional multi-authored textbook. Although it felt a bit like sacrilege to reduce one of the revered texts in our specialty to a “me too” multi-authored textbook, we agreed to take on the task.

The hybrid model developed for the fifth edition was undertaken by a small number of senior authors who were tasked with updating this classic text in their areas of expertise. This undertaking was daunting, but the model worked. We have maintained this structure for the sixth edition along with most of our authors.

We are proud to bring the sixth edition of *Stoelting’s Pharmacology & Physiology in Anesthetic Practice* to anesthesiology residents, clinicians, and investigators. We have tried to maintain the succinct elegance of Dr. Stoelting’s writing updated with the latest state-of-the-art knowledge and methods in anesthetic pharmacology and physiology.

Is everything in this book correct? No. The authors of each chapter have imperfect understanding; knowledge changes, and mistakes happen. Wikipedia brilliantly addresses this by allowing readers who catch errors to fix them. We can’t implement the “Wikipedia approach” in a textbook, but we can come close by inviting you, the reader compulsive enough to read the Preface, to bring any errors, corrections, or suggestions to our attention. We invite our readers to become “peer reviewers,” pointing us toward new information that should be included, out-of-date references, drugs no longer used, or missing content relevant to pharmacology and physiology in anesthesia practice. In this manner, readers will become collaborators for all future editions.

Finally, we have to acknowledge the efforts of our publishers, including Keith Donnellan, Ashley Fischer, Anthony Gonzalez, Tim Rinehart, and Harold Medina. No textbook comes to fruition without careful guidance, attention to detail, and occasional cajoling. In this case, they went full force on all three of us to maintain the gem that Bob Stoelting created.

*Pamela Flood, MD, MA
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[Dedication](#)

[Contributors](#)

[Foreword to the Sixth Edition](#)

[Preface to the Sixth Edition](#)

PART I

Basic Principles of Physiology and Pharmacology

1. Basic Principles of Physiology

Pamela Flood • Lisa Wise-Faberowski • Steven L. Shafer

[Body Composition](#)

[Blood Volume](#)

[Constituents of Body Fluid Compartments](#)

[Osmosis](#)

[Tonicity of Fluids](#)

[Fluid Management](#)

[Dehydration](#)

[Cell Structure and Function](#)

[Cell Anatomy](#)

[Cell Membrane](#)

[Transfer of Molecules Through Cell Membranes](#)

[Nucleus](#)

[Structure and Function of DNA and RNA](#)

[Cytoplasm](#)

[Mitochondria](#)

[Endoplasmic Reticulum](#)

[Lysosomes](#)

[Golgi Apparatus](#)

2. Basic Principles of Pharmacology

Pamela Flood • Steven L. Shafer

[Receptor Theory](#)

[Receptor Action](#)

[Receptor Types](#)

[Pharmacokinetics](#)

[Distribution](#)

[Protein Binding](#)

[Metabolism](#)

[Pathways of Metabolism](#)

[Phase I Enzymes](#)

[Phase II Enzymes](#)

[Hepatic Clearance](#)

[Renal Clearance](#)

[Absorption](#)

[Ionization](#)

[Determinants of Degree of Ionization](#)

[Ion Trapping](#)

[Route of Administration and Systemic Absorption of Drugs](#)

[Oral Administration](#)

[Sublingual, Buccal, and Nasal Administration](#)

[Transdermal Administration](#)

[Rectal Administration](#)
[Pharmacokinetic Models](#)
[Zero- and First-Order Processes](#)
[Physiologic Pharmacokinetic Models](#)
[Compartmental Pharmacokinetic Models](#)
[One-Compartment Model](#)
[Multicompartment Models](#)
[The Time Course of Drug Effect](#)
[Dose Calculations](#)
[Bolus Dosing](#)
[Maintenance Infusion Rate](#)
[Context-Sensitive Half-time](#)
[Pharmacodynamics](#)
[Concentration Versus Response Relationships](#)
[Potency and Efficacy](#)
[Effective Dose and Lethal Dose](#)
[Drug Interactions](#)
[Actions at Different Receptors](#)
[Stereochemistry](#)
[Clinical Aspects of Chirality](#)
[Individual Variability](#)
[Elderly Patients](#)
[Enzyme Activity](#)
[Genetic Disorders](#)
[Drug Interactions](#)

PART II

Neurologic System

3. Neurophysiology

Pamela Flood • Cassandra Bailey

How Nerves Work

Neurons

Classification of Afferent Nerve Fibers

Evaluation of Peripheral Nerve Function

The Action Potential

Propagation of Action Potentials

Ion Channel Evaluation

Abnormal Action Potentials

Neurotransmitters and Receptors

Ion Channels

Receptor Concentration

Receptor Diseases

The Synapse

Structure

Synaptic Fatigue

Posttetanic Facilitation

Factors That Influence Neuron Responsiveness

Central Nervous System

Cerebral Hemispheres

Anatomy of the Cerebral Cortex

Dominant Versus Nondominant Hemisphere

Memory

Awareness and Recall During Anesthesia

Postoperative Cognitive Dysfunction

Brainstem

Limbic System and Hypothalamus

Basal Ganglia

Reticular Activating System

Cerebellum

Spinal Cord

Gray Matter

White Matter

Pyramidal and Extrapyramidal Tracts

Thalamocortical System

Spinal Nerve

Central Nervous System Membranes

Autonomic Reflexes

Spinal Shock

Imaging of the Nervous System

Cerebral Blood Flow

Autoregulation

Electroencephalogram

Classification of Brain Waves

Clinical Uses

Brain Wave Monitors

Epilepsy

Evoked Potentials

Somatosensory Evoked Potentials

Motor Evoked Potentials

Auditory Evoked Potentials

Visual Evoked Potentials

Cerebrospinal Fluid

Formation

Reabsorption

Intracerebral Circulation

Hydrocephalus

Intracranial Pressure

Papilledema

Blood-Brain Barrier

Vision

Intraocular Pressure

Retina

Visual Pathway

Field of Vision

Muscular Control of Eye Movements

Innervation of the Eye

Horner Syndrome

Hearing

Perioperative Hearing Impairment

Taste

Smell

Nausea and Vomiting

[Peripheral Nervous System](#)
[Pathways for Peripheral Sensory Impulses](#)
[Pathways for Peripheral Motor Responses](#)
[Autonomic Nervous System](#)
[Anatomy of the Sympathetic Nervous System](#)
[Anatomy of the Parasympathetic Nervous System](#)
[Physiology of the Autonomic Nervous System](#)
[Norepinephrine as a Neurotransmitter](#)
[Acetylcholine as a Neurotransmitter](#)
[Residual Autonomic Nervous System Tone](#)
[Determination of Autonomic Nervous System Function](#)
[Adrenal Medulla](#)
[Synthesis](#)
[Release](#)
[Thermoregulation](#)
[Heat Loss](#)
[Regulation of Body Temperature](#)
[Nonshivering Thermogenesis](#)
[Shivering](#)
[Causes of Increased Body Temperature](#)
[Perioperative Temperature Changes](#)
[Sequence of Temperature Changes During Anesthesia](#)
[Beneficial Effects of Perioperative Hypothermia](#)
[Adverse Consequences of Perioperative Hypothermia](#)
[Perioperative Temperature Measurement](#)
[Prevention of Perioperative Hypothermia](#)
4. Inhaled Anesthetics
Pamela Flood • Steven L. Shafer • Ardin S. Berger
[History](#)
[Inhaled Anesthetics for the Present and Future](#)
[Cost Considerations](#)
[Current Clinically Useful Inhaled Anesthetics](#)
[Nitrous Oxide](#)
[Halothane](#)
[Enflurane](#)
[Isoflurane](#)
[Desflurane](#)
[Intraoperative Diagnosis of Carbon Monoxide Poisoning](#)
[Sevoflurane](#)
[Xenon](#)
[Pharmacokinetics of Inhaled Anesthetics](#)
[Determinants of Alveolar Partial Pressure](#)
[Inhaled Partial Pressure](#)
[Alveolar Ventilation](#)
[Anesthetic Breathing System](#)
[Solubility](#)
[Blood:Gas Partition Coefficients](#)
[Tissue:Blood Partition Coefficients](#)
[Oil:Gas Partition Coefficients](#)
[Nitrous Oxide Transfer to Closed Gas Spaces](#)
[Cardiopulmonary Bypass](#)

[Cardiac Output](#)
[Impact of a Shunt](#)
[Alveolar-to-Venous Partial Pressure Differences](#)
[Recovery From Anesthesia](#)
[Context-Sensitive Half-Time](#)
[Diffusion Hypoxia](#)
[Pharmacodynamics of Inhaled Anesthetics](#)
[Minimal Alveolar Concentration](#)
[Factors That Alter Minimal Alveolar Concentration](#)
[Mechanisms of Anesthetic Action](#)
[Meyer-Overton Theory \(Critical Volume Hypothesis\)](#)
[Stereoselectivity](#)
[Potential Mediators of Anesthetic Action](#)
[Mechanism of Immobility](#)
[Mechanism of Anesthesia-Induced Unconsciousness](#)
[Comparative Pharmacology of Gaseous Anesthetic Drugs](#)
[Central Nervous System Effects](#)
[Electroencephalogram](#)
[Seizure Activity](#)
[Evoked Potentials](#)
[Mental Function and Awareness](#)
[Cerebral Blood Flow](#)
[Cerebral Metabolic Oxygen Requirements](#)
[Cerebral Protection](#)
[Intracranial Pressure](#)
[Cerebrospinal Fluid Production](#)
[Circulatory Effects](#)
[Mean Arterial Pressure](#)
[Heart Rate](#)
[Cardiac Output and Stroke Volume](#)
[Right Atrial Pressure](#)
[Systemic Vascular Resistance](#)
[Pulmonary Vascular Resistance](#)
[Cardiac Dysrhythmias](#)
[Spontaneous Breathing](#)
[Coronary Blood Flow](#)
[Neurocirculatory Responses](#)
[Preexisting Diseases and Drug Therapy](#)
[Mechanisms of Circulatory Effects](#)
[Cardiac Protection \(Anesthetic Preconditioning\)](#)
[Ventilation Effects](#)
[Pattern of Breathing](#)
[Ventilatory Response to Carbon Dioxide](#)
[Surgical Stimulation](#)
[Duration of Administration](#)
[Mechanism of Depression](#)
[Management of Ventilatory Depression](#)
[Ventilatory Response to Hypoxemia](#)
[Airway Resistance and Irritability](#)
[Neurologic Effects](#)
[Hepatic Effects](#)

[Hepatic Blood Flow](#)
[Drug Clearance](#)
[Liver Function Tests](#)
[Hepatotoxicity](#)
[*Renal Effects*](#)
[Fluoride-Induced Nephrotoxicity](#)
[Skeletal Muscle Effects](#)
[Neuromuscular Junction](#)
[Malignant Hyperthermia](#)
[*Obstetric Effects*](#)
[Resistance to Infection](#)
[*Genetic Effects*](#)
[Bone Marrow Function](#)
[Peripheral Neuropathy](#)
[Total Body Oxygen Requirements](#)
[Metabolism](#)
[Environmental Impact of Inhaled Anesthetics](#)
[5. Intravenous Sedatives and Hypnotics](#)
James P. Rathmell • Albert Dahan
[Overview](#)
 [\$\gamma\$ -Aminobutyric Acid Agonists](#)
[Propofol](#)
[Commercial Preparations](#)
[Mechanism of Action](#)
[Pharmacokinetics](#)
[Clinical Uses](#)
[Effects on Organ Systems](#)
[Other Side Effects](#)
[Miscellaneous Effects](#)
[Etomidate](#)
[Commercial Preparation](#)
[Mechanism of Action](#)
[Pharmacokinetics](#)
[Clinical Uses](#)
[Side Effects](#)
[Benzodiazepines](#)
[*Mechanism of Action*](#)
[Nucleoside Transporter Systems](#)
[Electroencephalogram](#)
[Side Effects](#)
[Drug Interactions](#)
[Hypothalamic-Pituitary-Adrenal Axis](#)
[Dependence](#)
[Aging](#)
[Platelet Aggregation](#)
[Midazolam](#)
[Commercial Preparation](#)
[Pharmacokinetics](#)
[Effects on Organ Systems](#)
[Clinical Uses](#)
[Diazepam](#)

[Commercial Preparation](#)
[Effects on Organ Systems](#)
[Overdose](#)
[Clinical Uses](#)
[Lorazepam](#)
[Pharmacokinetics](#)
[Clinical Uses](#)
[Temazepam](#)
[Remimazolam](#)
[Flumazenil](#)
[Dose and Administration](#)
[Side Effects](#)
[Short-Acting Nonbenzodiazepine Benzodiazepines](#)
[Barbiturates](#)
[Barbiturates' Use in Anesthesia](#)
[Mechanism of Action](#)
[Pharmacokinetics](#)
[Pharmacodynamics and Clinical Applications](#)
[Side Effects](#)
[Other Effects](#)
[Non- \$\gamma\$ -Aminobutyric Acid Sedatives and Hypnotics](#)
[Ketamine](#)
[Structure-Activity Relationships](#)
[Mechanism of Action](#)
[Pharmacokinetics](#)
[Clinical Uses](#)
[Side Effects](#)
[Drug Interactions](#)
[Dextromethorphan](#)
[Dexmedetomidine](#)
[Pharmacokinetics](#)
[Clinical Uses](#)
[Effects on the Control of Breathing](#)
[6. Pain Physiology](#)
Hui Yang • Bihua Bie • Mohamed A. Naguib
[Social Impact](#)
[Neurobiology of Pain](#)
[Peripheral Nerve Physiology of Pain](#)
[Nociceptors \(Pain Receptors\)](#)
[Sensitization of Nociceptor](#)
[Primary Hyperalgesia and Secondary Hyperalgesia](#)
[Central Nervous System Physiology](#)
[The Dorsal Horn: The Relay Center for Nociception](#)
[Gate Theory](#)
[Central Sensitization of Dorsal Horn Neurons](#)
[Ascending Pathway for Pain Transmission](#)
[Supraspinal Modulation of Nociception](#)
[Descending Pathway for Pain Modulation](#)
[Transition From Acute Pain to Chronic Pain](#)
[Psychobiology of Pain](#)
[Some Specific Types of Pain](#)

[Neuropathic Pain](#)

[Visceral Pain](#)

[Complex Regional Pain Syndromes](#)

[Pain in Neonate and Infant](#)

[Embryologic Origin and Localization of Pain](#)

[7. Opioid Agonists and Antagonists](#)

Kenneth C. Cummings III • Mohamed A. Naguib

[Chemical Structure of Opium Alkaloids](#)

[Semisynthetic Opioids](#)

[Synthetic Opioids](#)

[Opioid Receptors](#)

[Endogenous Pain-Modulating Mechanisms](#)

[Common Opioid Side Effects](#)

[Cardiovascular System](#)

[Ventilation](#)

[Cough Suppression](#)

[Central Nervous System](#)

[Rigidity](#)

[Sedation](#)

[Biliary Tract](#)

[Gastrointestinal Tract](#)

[Nausea and Vomiting](#)

[Genitourinary System](#)

[Cutaneous Changes](#)

[Placental Transfer](#)

[Drug Interactions](#)

[Hormonal Changes](#)

[Overdose](#)

[Provocation of Coughing](#)

[Pharmacodynamic Tolerance and Physical Dependence](#)

[Opioid Agonists](#)

[Morphine](#)

[Pharmacokinetics](#)

[Side Effects](#)

[Meperidine](#)

[Pharmacokinetics](#)

[Clinical Uses](#)

[Side Effects](#)

[Fentanyl](#)

[Pharmacokinetics](#)

[Clinical Uses](#)

[Side Effects](#)

[Sufentanil](#)

[Pharmacokinetics](#)

[Clinical Uses](#)

[Alfentanil](#)

[Pharmacokinetics](#)

[Clinical Uses](#)

[Remifentanil](#)

[Ventilation](#)

[Pharmacokinetics](#)

[Clinical Uses](#)
[Side Effects](#)
[Opioids With Oral Bioavailability](#)
[Codeine](#)
[Hydromorphone](#)
[Oxymorphone](#)
[Oxycodone](#)
[Hydrocodone](#)
[Methadone](#)
[Opioid Withdrawal](#)
[Treatment of Chronic Pain](#)
[Tramadol](#)
[Heroin](#)
[Opioid Agonist-Antagonists](#)
[Pentazocine](#)
[Clinical Uses](#)
[Side Effects](#)
[Butorphanol](#)
[Side Effects](#)
[Nalbuphine](#)
[Buprenorphine](#)
[Side Effects](#)
[Opioid Antagonists](#)
[Naloxone](#)
[Side Effects](#)
[Role in Treatment of Shock](#)
[Antagonism of General Anesthesia](#)
[Naltrexone](#)
[Methylnaltrexone](#)
[Alvimopan](#)
[Naloxegol](#)
[Tamper- or Abuse-Resistant Opioids](#)
[Opioid Allergy](#)
[Opioid Immune Modulation](#)
[Anesthetic Requirements](#)
[Patient-Controlled Analgesia](#)
[Neuraxial Opioids](#)
[Pharmacokinetics](#)
[Side Effects](#)
[Pruritus](#)
[Urinary Retention](#)
[Depression of Ventilation](#)
[Sedation](#)
[Central Nervous System Excitation](#)
[Viral Reactivation](#)
[Neonatal Morbidity](#)
[Miscellaneous Side Effects](#)
[Opioid Safety Issues](#)
[Obstructive Sleep Apnea](#)
[Practical Issues](#)
[The “Opioid Crisis”](#)

8. Centrally Acting Nonopiod Analgesics

Chihiro Toda • Mohamed A. Naguib

α_2 -Adrenergic Agonists

Clonidine

Dexmedetomidine

Neostigmine

Ketamine

Tramadol

Droperidol

Conopeptides

Ziconotide

Other Investigational Conopeptides

CGX-1160

Octreotide

Baclofen

Cyclooxygenase Inhibitors

Ketorolac

Magnesium Sulfate

Conclusion

9. Peripherally Acting Analgesics

Chihiro Toda • Mohamed A. Naguib

Nonsteroidal Antiinflammatory Drugs

Less Selective Nonsteroidal Antiinflammatory Drugs

Side Effects of Nonsteroidal Antiinflammatory Drugs

Platelet Function

Gastrointestinal Side Effects

Cardiovascular Side Effects

Renal Side Effects

Liver Side Effects

Pulmonary Side Effects

Hypersensitivity Reactions

Idiosyncratic Adverse Effects

Drug-Drug Interactions With Nonsteroidal Antiinflammatory Drugs

Acetaminophen

Acetylsalicylic Acid (Aspirin)

Overdose

Steroids

Systemic Local Anesthetics

Topical Application of 5% Lidocaine

Capsaicin

Ketamine

Clonidine

Dexmedetomidine

Opioids

10. Local Anesthetics

Kamal Maheshwari • Mohamed A. Naguib

Molecular Structure

Structure-Activity Relationships

Racemic Mixtures or Pure Isomers

Mechanism of Action

Sodium Channels

[Frequency-Dependent Blockade](#)
[Other Site of Action Targets](#)
[Minimum Effective Concentration](#)
[Differential Conduction Blockade](#)
[Pharmacokinetics](#)
[Absorption and Distribution](#)
[Lung Extraction](#)
[Changes During Pregnancy](#)
[Placental Transfer](#)
[Renal Elimination and Clearance](#)
[Metabolism of Amide Local Anesthetics](#)
[Lidocaine](#)
[Prilocaine](#)
[Mepivacaine](#)
[Bupivacaine](#)
[Ropivacaine](#)
[Dibucaine](#)
[Metabolism of Ester Local Anesthetics](#)
[Procaine](#)
[Chloroprocaine](#)
[Tetracaine](#)
[Benzocaine](#)
[Cocaine](#)
[Alkalinization of Local Anesthetic Solutions](#)
[Adjuvant Mixed With Local Anesthetics](#)
[Combinations of Local Anesthetics](#)
[Use of Vasoconstrictors](#)
[Adverse Effects of Local Anesthetics](#)
[Allergic Reactions](#)
[Cross-Sensitivity](#)
[Documentation of Allergy](#)
[Local Anesthetic Systemic Toxicity](#)
[Central Nervous System Effects](#)
[Cardiovascular System Effects](#)
[Treatment of Local Anesthetic Systemic Toxicity.](#)
[Neural Tissue Toxicity \(Neurotoxicity\).](#)
[Transient Neurologic Symptoms](#)
[Cauda Equina Syndrome](#)
[Anterior Spinal Artery Syndrome](#)
[Methemoglobinemia](#)
[Ventilatory Response to Hypoxia](#)
[Hepatotoxicity](#)
[Uses of Local Anesthetics](#)
[Regional Anesthesia](#)
[Topical Anesthesia](#)
[Local Infiltration](#)
[Peripheral Nerve Block Anesthesia](#)
[Continuous Peripheral Nerve Blocks](#)
[Intravenous Regional Anesthesia \(Bier Block\)](#)
[Epidural Anesthesia](#)
[Spinal Anesthesia](#)

[Liposomal Local Anesthetics](#)

[Tumescent Liposuction](#)

[Cocaine Toxicity](#)

[Pharmacokinetics](#)

[Adverse Physiologic Effects](#)

[Treatment](#)

[11. Neuromuscular Physiology.](#)

Mohamed A. Naguib

[Muscle Types](#)

[Motor Units](#)

[The Neuromuscular Junction](#)

[Presynaptic Region](#)

[Synaptic Vesicles](#)

[Synaptic Cleft](#)

[The Nicotinic Acetylcholine Receptor at the Neuromuscular Junction](#)

[Neuromuscular Transmission and Excitation-Contraction Coupling](#)

[Blood Flow](#)

[Smooth Muscle](#)

[Mechanism of Contraction](#)

[Uterine Smooth Muscle](#)

[12. Neuromuscular-Blocking Drugs and Reversal Agents](#)

Mohamed A. Naguib

[Principles of Action of Neuromuscular-Blocking Drugs at the Neuromuscular Junction](#)

[Pharmacology of Succinylcholine](#)

[Structure-Activity Relationships for Succinylcholine](#)

[Pharmacokinetics, Pharmacodynamics, and Pharmacogenomics of Succinylcholine](#)

[Factors Affecting Butyrylcholinesterase Activity](#)

[Genetic Variants of Butyrylcholinesterase](#)

[Side Effects of Succinylcholine](#)

[Cardiovascular Effects](#)

[Hyperkalemia](#)

[Myoglobinuria](#)

[Increased Intraocular Pressure](#)

[Increased Intragastric Pressure](#)

[Increased Intracranial Pressure](#)

[Myalgias](#)

[Masseter Spasm](#)

[Pharmacology of Nondepolarizing Neuromuscular-Blocking Drugs](#)

[Benzylisoquinolinium Compounds](#)

[Atracurium](#)

[Cisatracurium](#)

[Mivacurium](#)

[Steroidal Compounds](#)

[Pancuronium](#)

[Vecuronium](#)

[Rocuronium](#)

[Potency of Nondepolarizing Neuromuscular-Blocking Drugs](#)

[Effect of Drug Potency on Speed of Onset](#)

[Factors That Increase the Potency of Nondepolarizing Neuromuscular-Blocking Drugs](#)

[Factors That Decrease the Potency of Nondepolarizing Neuromuscular-Blocking Drugs](#)

[Adverse Effects of Nondepolarizing Neuromuscular-Blocking Drugs](#)

[Autonomic Effects](#)

[Histamine Release](#)

[Allergic Reactions](#)

[Drugs for Reversal of Nondepolarizing Neuromuscular Blockade](#)

[Acetylcholinesterase at the Neuromuscular Junction](#)

[Mechanisms of Action of Acetylcholinesterase Inhibitors](#)

[Clinical Pharmacology](#)

[Limitations of Acetylcholinesterase Inhibitors](#)

[Sugammadex: A Selective Relaxant Binding Agent](#)

[13. Neurologically Active Drugs](#)

Mark Alexander Burbridge • Pamela Flood

[Antiepileptic Drugs](#)

[Pharmacokinetics](#)

[Drug Interactions Related to Protein Binding](#)

[Drug Interactions Related to Accelerated Metabolism](#)

[Principles of Dosing](#)

[Plasma Concentrations and Laboratory Testing](#)

[Mechanism of Seizure Activity](#)

[Mechanism of Drug Action](#)

[Major Antiepileptic Drugs](#)

[Adverse Side Effects](#)

[Carbamazepine](#)

[Esllicarbazepine](#)

[Ethosuximide](#)

[Felbamate](#)

[Gabapentin](#)

[Lacosamide](#)

[Lamotrigine](#)

[Levetiracetam](#)

[Oxcarbazepine](#)

[Perampanel](#)

[Phenobarbital](#)

[Phenytoin](#)

[Primidone](#)

[Rufinamide](#)

[Stiripentol](#)

[Tiagabine](#)

[Topiramate](#)

[Valproic Acid](#)

[Vigabatrin](#)

[Zonisamide](#)

[Benzodiazepines](#)

[Status Epilepticus](#)

[Treatment](#)

[Drugs Used for Treatment of Parkinson Disease](#)

[Levodopa](#)

[Metabolism](#)

[Side Effects](#)

[Laboratory Measurements](#)

[Drug Interactions](#)

[Peripheral Decarboxylase Inhibitors](#)

[Catechol-O-methyltransferase Inhibitors](#)
[Side Effects](#)
[Synthetic Dopamine Agonists](#)
[Side Effects](#)
[Anticholinergic Drugs](#)
[Amantadine](#)
[Monoamine Oxidase Type B Enzyme Inhibitors](#)
[Nonpharmacologic Treatment](#)
[Central Nervous System Stimulants](#)
[Amphetamine](#)
[Doxapram](#)
[Clinical Uses](#)
[Methylphenidate](#)
[Methylxanthines](#)
[Mechanism of Action](#)
[Clinical Uses](#)
[Toxicity](#)
[Drug Interactions](#)
[Caffeine](#)
[Almitrine](#)
[Modafinil](#)
[Centrally Acting Muscle Relaxants](#)
[Baclofen](#)
[Benzodiazepines](#)
[Botulinum Toxin](#)
[Tizanidine](#)
[Dantrolene](#)

PART III

[Circulatory System](#)

[14. Circulatory Physiology](#)

James Ramsay

[Systemic Circulation](#)

[Endothelial Function](#)

[Endothelial Function and Regulation of Vascular Tone](#)

[Components of the Systemic Circulation](#)

[Arteries](#)

[Arterioles](#)

[Capillaries](#)

[Venules and Veins](#)

[Physical Characteristics of the Systemic Circulation](#)

[Measurement of Systemic Blood Pressure](#)

[Direct Measurement of Blood Pressure With an Intravascular Catheter](#)

[Progressive Declines in Systemic Blood Pressure](#)

[Pulse Pressure in Arteries](#)

[The Venous Circulation](#)

[Right Atrial Pressure](#)

[Measuring Central Venous Pressure](#)

[Effect of Hydrostatic Pressure](#)

[Venous Valves and the Pump Mechanism](#)

[Blood Viscosity](#)

[Determinants of Tissue Blood Flow](#)
[Vascular Distensibility](#)
[Vascular Compliance](#)
[Control of Tissue Blood Flow](#)
[Local Control of Blood Flow](#)
[Autoregulation of Blood Flow](#)
[Long-Term Control of Blood Flow](#)
[Autonomic Nervous System Control of Blood Flow](#)
[Hormone Control of Blood Flow](#)
[Regulation of Systemic Blood Pressure](#)
[Rapid-Acting Mechanisms for the Regulation of Systemic Blood Pressure](#)
[Moderately Rapid-Acting Mechanisms for the Regulation of Systemic Blood Pressure](#)
[Long-Term Mechanisms for the Regulation of Systemic Blood Pressure](#)
[Regulation of Cardiac Output and Venous Return](#)
[Determinants of Cardiac Output](#)
[Ventricular Function Curves](#)
[Pressure-Volume Loops](#)
[Shock Syndromes](#)
[Measurement of Cardiac Output](#)
[Microcirculation](#)
[Anatomy of the Microcirculation](#)
[Blood Flow in Capillaries](#)
[Vasoactive Role of the Capillary Endothelium](#)
[Fluid Movement Between the Capillary Lumen and the Interstitium](#)
[Lymphatics](#)
[Anatomy](#)
[Formation and Flow of Lymph](#)
[Edema](#)
[Pulmonary Circulation](#)
[Anatomy](#)
[Bronchial Circulation](#)
[Pulmonary Lymph Vessels](#)
[Pulmonary Vascular Pressure](#)
[Measurement of Left Atrial Pressure](#)
[Interstitial Fluid Space](#)
[Pulmonary Blood Volume](#)
[Pulmonary Blood Flow and Distribution](#)
[Endothelial Regulation of Pulmonary Blood Flow](#)
[Hypoxic Pulmonary Vasoconstriction](#)
[Effect of Breathing](#)
[Regional Blood Flow in the Lungs](#)
[Pulmonary Circulatory Pathology](#)
[Pulmonary Edema](#)
[Pulmonary Embolism](#)
[Pulmonary Hypertension](#)
[15. Cardiac Physiology](#).
Teresa A. Mulaikal • Andrea N. Miltiades Sumeet Goswami • Bessie Kachulis
[Cardiac Anatomy](#)
[Pericardium](#)
[Heart](#)
[The Coronary Circulation](#)

[The Cardiac Conduction System](#)

[Cardiac Physiology](#)

[Myocardium](#)

[Cardiac Action Potential](#)

[Excitation-Contraction Coupling](#)

[Control of Cardiac Function](#)

[Cardiac Cycle](#)

[Electrical and Mechanical Events](#)

[Myocardial Performance, Preload, and Afterload](#)

[Hemodynamic Calculations](#)

[Pathophysiology](#)

[Ischemic Heart Disease](#)

[Heart Failure](#)

[Valvular Heart Disease](#)

[Aortic Stenosis](#)

[Aortic Insufficiency](#)

[Mitral Stenosis](#)

[Mitral Regurgitation](#)

[Cardiac Dysrhythmias](#)

[Etiology](#)

[Mechanisms of Arrhythmia](#)

[Types of Dysrhythmias](#)

[16. Renal Physiology](#)

Brian Chang • Jonathan Hastie

[Kidney Structure and Function](#)

[Basic Anatomy of the Kidney](#)

[The Glomerulus](#)

[The Renal Tubule](#)

[Renal Blood Flow](#)

[Renal Cortex Blood Flow: Glomerular and Peritubular Capillaries](#)

[Renal Medulla Blood Flow: The Vasa Recta](#)

[Autoregulation of Renal Blood Flow](#)

[Juxtaglomerular Apparatus](#)

[Regulation of Body Fluid](#)

[Blood and Extracellular Fluid Volume](#)

[Atrial and Renal Natriuretic Factors](#)

[Osmolarity of Body Fluids](#)

[Osmoreceptor–Arginine Vasopressin Hormone](#)

[Thirst Reflex](#)

[Plasma Concentration of Ions and Urea](#)

[Sodium](#)

[Potassium](#)

[Acid-Base Balance](#)

[Calcium and Magnesium](#)

[Urea](#)

[Measuring Kidney Function](#)

[Acute Kidney Injury](#)

[Classification](#)

[Prerenal Azotemia](#)

[Intrinsic Causes of Acute Kidney Injury](#)

[Postrenal Obstructive Nephropathy](#)

[Acute Kidney Injury Diagnosis](#)

[Diagnostic Criteria](#)

[Anesthesia and the Kidneys](#)

[Anesthesia and Renal Blood Flow](#)

[Perioperative Risk Assessment](#)

[Intraoperative Management](#)

[17. Intravenous Fluids and Electrolytes](#)

Emily P. Wang • Jessica Spellman

[Total Body Fluid Composition](#)

[Intravenous Fluid Types](#)

[Crystalloids](#)

[Colloids](#)

[Albumin \(4%-5%\)](#)

[Semisynthetic Colloid Solutions](#)

[Assessing Fluid Responsiveness](#)

[Important Fluid Constituents](#)

[Magnesium](#)

[Role of Magnesium](#)

[Hypomagnesemia](#)

[Hypermagnesemia](#)

[Preeclampsia](#)

[Cardiac Dysrhythmias](#)

[Analgesia](#)

[Asthma](#)

[Pheochromocytoma](#)

[Calcium](#)

[Role of Calcium](#)

[Hypocalcemia](#)

[Hypercalcemia](#)

[Bone Composition](#)

[Denosumab](#)

[Potassium](#)

[Role of Potassium](#)

[Drugs Causing Hypokalemia](#)

[Drugs Causing Hyperkalemia](#)

[Hypokalemia](#)

[Hyperkalemia](#)

[Phosphate](#)

[Iron](#)

[Iron Deficiency](#)

[Copper](#)

[Zinc](#)

[Chromium](#)

[Selenium](#)

[Manganese](#)

[Molybdenum](#)

[18. Sympathomimetic Drugs](#)

Javier Lorenzo

[Naturally Occurring Catecholamines](#)

[Epinephrine](#)

[Clinical Uses](#)

[Cardiovascular Effects](#)
[Airway Smooth Muscle](#)
[Metabolic Effects](#)
[Electrolytes](#)
[Ocular Effects](#)
[Gastrointestinal and Genitourinary Effects](#)
[Norepinephrine](#)
[Clinical Uses](#)
[Side Effects](#)
[Dopamine](#)
[Clinical Uses](#)
[Renal-Dose Dopamine](#)
[Cardiovascular Effects](#)
[Gastrointestinal Effects](#)
[Endocrine and Immunologic Effects](#)
[Respiratory Effects](#)
[Intraocular Pressure](#)
[Synthetic Catecholamines](#)
[Isoproterenol](#)
[Clinical Uses](#)
[Adverse Effects](#)
[Dobutamine](#)
[Clinical Uses](#)
[Adverse Effects](#)
[Synthetic Noncatecholamines](#)
[Ephedrine](#)
[Clinical Uses](#)
[Cardiovascular Effects](#)
[Phenylephrine](#)
[Clinical Uses](#)
[Cardiovascular Effects](#)
[Treatment of Overdose](#)
[Selective \$\beta_2\$ -Adrenergic Agonists](#)
[Clinical Uses](#)
[Route of Administration](#)
[Side Effects](#)
[Albuterol](#)
[Metaproterenol](#)
[Terbutaline](#)
[Cardiac Glycosides](#)
[Digoxin](#)
[Pharmacokinetics](#)
[Mechanism of Action](#)
[Toxicity](#)
[Drug Interactions](#)
[Selective Phosphodiesterase Inhibitors](#)
[Milrinone](#)
[Clinical Uses](#)
[Side Effects](#)
[Calcium](#)
[Calcium Measurement](#)

[Calcium Sensitizers](#)

[Levosimendan](#)

[19. Sympatholytics](#)

Steven E. Miller

[\$\alpha\$ - and \$\beta\$ -Adrenergic Receptor Antagonists](#)

[\$\alpha\$ -Adrenergic Receptor Antagonists](#)

[Mechanism of Action](#)

[Phentolamine](#)

[Phenoxybenzamine](#)

[Yohimbine](#)

[Doxazosin](#)

[Prazosin](#)

[Terazosin](#)

[Tamsulosin](#)

[Alfuzosin](#)

[Sildosin](#)

[Tolazoline](#)

[\$\alpha_2\$ -Adrenergic Receptor Agonists](#)

[Mechanism of Action](#)

[Clonidine](#)

[Dexmedetomidine](#)

[\$\beta\$ -Adrenergic Receptor Antagonists](#)

[Mechanism of Action](#)

[Structure-Activity Relationships](#)

[Classification](#)

[Pharmacokinetics](#)

[Propranolol](#)

[Nadolol and Pindolol](#)

[Timolol](#)

[Metoprolol](#)

[Atenolol](#)

[Betaxolol](#)

[Bisoprolol](#)

[Nebivolol](#)

[Esmolol](#)

[Combined \$\alpha\$ - and \$\beta\$ -Adrenergic Receptor Antagonists](#)

[Labetalol](#)

[Carvedilol](#)

[Calcium Channel Blockers](#)

[Mechanism of Action](#)

[Pharmacologic Effects](#)

[Phenylalkylamines](#)

[Verapamil](#)

[Dihydropyridines](#)

[Nifedipine](#)

[Nicardipine](#)

[Clevidipine](#)

[Nimodipine](#)

[Amlodipine](#)

[Benzothiazepines](#)

[Diltiazem](#)

[Drug Interactions](#)

[Anesthetic Drugs](#)

[Neuromuscular Blocking Drugs](#)

[Potassium-Containing Solutions](#)

[Platelet Function](#)

[Digoxin](#)

[H₂ Antagonists](#)

[Cytoprotection](#)

[20. Vasodilators](#)

Thomas J. Krall • James Ramsay

[Introduction](#)

[Systemic Hypertension](#)

[Specific Antihypertensive Drugs and Anesthesia](#)

[β-Adrenergic Blockers](#)

[Mechanism of Action](#)

[Side Effects](#)

[Intravenous β Blockers](#)

[α₁ Receptor Blockers](#)

[Pharmacokinetics](#)

[Cardiovascular Effects](#)

[Side Effects](#)

[α₂ Agonists](#)

[Mechanism of Action](#)

[Pharmacokinetics](#)

[Cardiovascular Effects](#)

[Side Effects](#)

[Rebound Hypertension](#)

[Other Clinical Uses](#)

[Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers](#)

[Mechanism of Action](#)

[Side Effects](#)

[Preoperative Management](#)

[Specific Agents](#)

[Calcium Channel Blocking Drugs](#)

[Phosphodiesterase Inhibitors](#)

[Nitric Oxide and Nitrovasodilators](#)

[Nitric Oxide](#)

[Nitric Oxide as a Pulmonary Vasodilator](#)

[Toxicity](#)

[Nitrodilators](#)

[Sodium Nitroprusside](#)

[Nitrates](#)

[Isosorbide Dinitrate](#)

[Hydralazine](#)

[Fenoldopam](#)

[Diuretics](#)

[Drugs Not Discussed](#)

[21. Antiarrhythmic Drugs](#)

Wendy Smith • James Ramsay

[Mechanism of Action](#)

[Classification](#)

[Class I Drugs](#)

[Class IA Drugs](#)

[Class IB Drugs](#)

[Class IC Drugs](#)

[Class II Drugs](#)

[Class III Drugs](#)

[Class IV Drugs](#)

[Class O Drugs](#)

[Proarrhythmic Effects](#)

[Torsades de Pointes](#)

[Incessant Ventricular Tachycardia](#)

[Wide Complex Ventricular Rhythm](#)

[Efficacy and Results of Treatment With Cardiac Antiarrhythmic Drugs](#)

[Prophylactic Antiarrhythmic Drug Therapy](#)

[Decision to Treat Cardiac Arrhythmias](#)

[Antiarrhythmic Drug Pharmacology](#)

[Quinidine](#)

[Mechanism of Action](#)

[Metabolism and Excretion](#)

[Side Effects](#)

[Procainamide](#)

[Mechanism of Action](#)

[Metabolism and Excretion](#)

[Side Effects](#)

[Disopyramide](#)

[Side Effects](#)

[Moricizine](#)

[Side Effects](#)

[Lidocaine](#)

[Mechanism of Action](#)

[Metabolism and Excretion](#)

[Side Effects](#)

[Mexiletine](#)

[Side Effects](#)

[Tocainide](#)

[Phenytoin](#)

[Mechanism of Action](#)

[Metabolism and Excretion](#)

[Side Effects](#)

[Flecainide](#)

[Metabolism and Excretion](#)

[Side Effects](#)

[Propafenone](#)

[Side Effects](#)

[\$\beta\$ -Adrenergic Antagonists](#)

[Mechanism of Action](#)

[Metabolism and Excretion](#)

[Side Effects](#)

[Amiodarone](#)

[Mechanism of Action](#)

[Metabolism and Excretion](#)

[Side Effects](#)

[Pharmacokinetic](#)

[Dronedarone](#)

[Mechanism of Action](#)

[Metabolism and Excretion](#)

[Side Effects](#)

[Sotalol](#)

[Side Effects](#)

[Ibutilide](#)

[Dofetilide](#)

[Verapamil and Diltiazem](#)

[Mechanism of Action](#)

[Metabolism and Excretion](#)

[Side Effects](#)

[Other Cardiac Antiarrhythmic Drugs](#)

[Digitalis](#)

[Adenosine](#)

[Mechanism of Action](#)

[Side Effects](#)

[Ranolazine](#)

[22. Diuretics 535](#)

Vikram V. Saxena • Maya Jalbout Hastie

[Carbonic Anhydrase Inhibitors](#)

[Pharmacokinetics and Pharmacodynamics](#)

[Clinical Uses](#)

[Side Effects](#)

[Loop Diuretics](#)

[Pharmacokinetics and Pharmacodynamics](#)

[Ethacrynic Acid](#)

[Furosemide](#)

[Bumetanide and Torsemide](#)

[Clinical Uses](#)

[Side Effects](#)

[Thiazide Diuretics](#)

[Pharmacokinetics and Pharmacodynamics](#)

[Clinical Uses](#)

[Side Effects](#)

[Osmotic Diuretics](#)

[Mannitol](#)

[Pharmacokinetics and Pharmacodynamics](#)

[Clinical Uses](#)

[Side Effects](#)

[Potassium-Sparing Diuretics](#)

[Pharmacokinetics and Pharmacodynamics](#)

[Clinical Uses](#)

[Side Effects](#)

[Aldosterone Antagonists](#)

[Pharmacokinetics and Pharmacodynamics](#)

[Clinical Uses](#)

[Side Effects](#)

[Dopamine Receptor Agonists](#)

[Pharmacokinetics and Pharmacodynamics](#)

[Clinical Uses](#)

[Natriuretic Peptides](#)

[Vasopressin Receptor Antagonists](#)

[Pharmacokinetics and Pharmacodynamics](#)

[Clinical Uses](#)

[Side Effects](#)

[Aquaporin Modulators](#)

[23. Lipid-Lowering Drugs](#)

Peter C. Schmidt

[Lipoprotein Metabolism](#)

[Exogenous Pathway](#)

[Endogenous Pathway](#)

[Lipid Disorders](#)

[Drugs for Treatment of Hyperlipidemia](#)

[Statins](#)

[Pharmacokinetics](#)

[Side Effects](#)

[Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors](#)

[Pharmacokinetics](#)

[Side Effects](#)

[Bile Acid Resins](#)

[Side Effects](#)

[Niacin](#)

[Pharmacokinetics](#)

[Side Effects](#)

[Fibrates](#)

[Pharmacokinetics](#)

[Side Effects](#)

[Ezetimibe](#)

[Side Effects](#)

[Omega-3 Fatty Acids \(Fish Oil\)](#)

[Other Agents](#)

PART IV

Pulmonary System

[24. Gas Exchange](#)

Alexander Huang • Peter Slinger

[Functional Anatomy](#)

[Upper Airway Anatomy and Gas Flow](#)

[Oropharynx and Nasopharynx](#)

[Larynx](#)

[Pharyngeal Innervation](#)

[Upper Airway Gas Flow](#)

[Tracheal and Bronchial Structure](#)

[Respiratory Airways and Alveoli](#)

[Pulmonary Circulation](#)

[Thorax and Muscles of Respiration](#)

[Inhalation](#)

[Expiration](#)

[Respiratory Mechanical Function](#)

[Lung Volumes and Spirometry](#)
[Closing Capacity and Closing Volume](#)
[Compliance](#)
[Resistance](#)
[The Equal Pressure Point](#)
[Work of Breathing](#)
[Respiratory Fatigue](#)
[Physiology of Ventilation and Perfusion](#)
[Pulmonary Circulation](#)
[Pulmonary Hemodynamics](#)
[Distribution of Perfusion](#)
[Matching of Ventilation and Perfusion](#)
[Dead Space](#)
[Measurement of Dead Space](#)
[Shunt](#)
[Alveolar-Arterial Oxygen Difference \(\$A-aDo_2\$ \)](#)
[Hypoxic Pulmonary Vasoconstriction](#)
[Movement of Gas](#)
[Oxygen Transport](#)
[Shifts of the Oxyhemoglobin Dissociation Curve](#)
[Carbon Dioxide Transport](#)
[Control of Respiration](#)
[Central Nervous System](#)
[Peripheral Chemoreceptors](#)
[Other Neural Connections to the Medullary Respiratory Centers](#)
[Abnormal Breathing Patterns](#)
[Altered Physiologic Conditions](#)
[Anesthesia](#)
[Position](#)
[Obesity](#)
[Sleep-Disordered Breathing](#)
[Exercise](#)
[Altered Barometric Pressures](#)
[Age](#)
[Infants and Children](#)
[The Elderly](#)
[Chronic Respiratory Disease](#)
[One-Lung Ventilation](#)
[Extracorporeal Ventilatory Support](#)
[25. Respiratory Pharmacology](#)
Peter Slinger
[Pharmacology of the Airways](#)
[Influence of the Autonomic Nervous System on the Airways](#)
[Inhaled Adrenergic Agonists](#)
[Systemic Adrenergic Agonists](#)
[Inhaled Cholinergic Antagonists](#)
[Systemic Cholinergic Antagonists](#)
[Influence of Inflammation on the Airway](#)
[Inhaled Corticosteroids](#)
[Systemic Corticosteroids](#)
[Leukotriene Modifiers](#)

[Mast Cell Stabilizers](#)
[Methylxanthines](#)
[Combined Pharmacologic Therapy of Asthma](#)
[Influence of Anesthetics on the Airways](#)
[Volatile Anesthetics](#)
[Intravenous Anesthetics](#)
[Local Anesthetics](#)
[Influence of Adjunctive Agents on the Airway](#)
[Pharmacology of the Pulmonary Circulation](#)
[Anesthetic Drugs](#)
[Ketamine](#)
[Propofol](#)
[Etomidate](#)
[Opioids](#)
[Volatile Anesthetics](#)
[Neuromuscular Blockers](#)
[Magnesium](#)
[Regional Analgesia](#)
[Vasopressors and Inotropes](#)
[Pulmonary Vasodilators](#)
[Nitric Oxide](#)
[Prostaglandins](#)
[Phosphodiesterase Inhibitors](#)
[Hypoxic Pulmonary Vasoconstriction](#)
[Intrinsic Pharmacologic Effects of the Lungs](#)
[Exogenous Substances](#)
[Drugs](#)
[Opioids](#)
[Local Anesthetics](#)
[Hypnotics](#)
[Endogenous Substances](#)
[Angiotensin-Converting Enzyme](#)
[Biogenic Amines](#)
[Arachidonic Acid Metabolites](#)
[26. Acid–Base Disorders](#)
Peter Slinger
[Mechanisms for Regulation of Hydrogen Ion Concentration](#)
[Buffer Systems](#)
[Bicarbonate Buffering System](#)
[Hemoglobin Buffering System](#)
[Protein Buffering System](#)
[Phosphate Buffering System](#)
[Intracellular pH Regulation](#)
[Ventilatory Responses](#)
[Renal Responses](#)
[Classification of Acid–Base Disturbances](#)
[Respiratory Acidosis](#)
[Respiratory Alkalosis](#)
[Metabolic Acidosis](#)
[Lactic Acidosis](#)
[Dilutional Acidosis](#)

[Other Causes of Metabolic Acidosis](#)
[Differential Diagnosis of Metabolic Acidosis](#)
[Base Excess](#)
[Anion Gap](#)
[Strong Ion Gap](#)
[Simplified Approach to Metabolic Acidosis of Uncertain Etiology](#)
[Metabolic Alkalosis](#)
[Compensation for Acid–Base Disturbances](#)
[Effects of Temperature on Acid–Base Status](#)
[pH-Stat Management](#)
[α-Stat Management](#)

PART V

Blood and Hemostasis

[27. Physiology of Blood and Hemostasis](#)
Jerrold H. Levy
[Hemostasis and History](#)
[Initiation of Coagulation](#)
[Propagation of Coagulation](#)
[Tissue Factor, Thrombin, and Fibrin\(ogen\) in Clot Formation and Stability](#)
[Endothelial Regulation of Coagulation](#)
[Antithrombin and Proteins C and S](#)
[Inflammation and Coagulation: An Important Link](#)
[Coagulation Testing](#)
[Perioperative Changes in Coagulation](#)
[Hemostatic Therapy](#)
[Postoperative Hypercoagulability](#)
[Disseminated Intravascular Coagulation](#)
[Conclusion](#)

28. Blood Products and Blood Components

Jerrold H. Levy
[Transfusion Therapy for Bleeding](#)
[Red Blood Cells](#)
[Red Blood Cell Storage Lesions](#)
[Red Blood Cell Storage and Tissue Oxygenation Parameters](#)
[Plasma/Fresh Frozen Plasma](#)
[Solvent/Detergent-Treated Plasma](#)
[Cryoprecipitate](#)
[Platelet Concentrates](#)
[Alloimmunization](#)
[Leukoreduction](#)
[Graft Versus Host Disease](#)
[Indications for Platelet Transfusions and Transfusion Triggers](#)
[Purified Factor Concentrates](#)
[Fibrinogen Concentrates](#)
[Prothrombin Complex Concentrates](#)
[von Willebrand Factor](#)
[Hereditary Angioedema and C1 Esterase Inhibitor Concentrates](#)
[Adverse Effects of Transfusions](#)
[Transfusion as an Inflammatory Response](#)
[Transfusion-Associated Circulatory Overload](#)

[Transfusion-Related Acute Lung Injury](#)

[Clinical History of Transfusion-Related Acute Lung Injury](#)

[Multiple Factors Influence Transfusion-Related Acute Lung Injury](#)

[Acute Pulmonary Edema and Management](#)

[Decreasing the Incidence of Transfusion-Related Acute Lung Injury](#)

[Plasma From Male Donors](#)

[Transfusion-Related Acute Inflammatory Responses and Immunomodulation](#)

[Role of Neutrophils and Other Inflammatory Cells](#)

[Summary](#)

[29. Procoagulants](#)

Jerrold H. Levy

[Antifibrinolytic Agents: Lysine Analogs](#)

[Antifibrinolytic Agents: Aprotinin](#)

[Protamine](#)

[Desmopressin](#)

[Fibrinogen](#)

[Recombinant Coagulation Products and Factor Concentrates](#)

[Recombinant Activated Factor VIIa](#)

[Factor XIII](#)

[Prothrombin Complex Concentrates](#)

[Topical Hemostatic Agents](#)

[Summary](#)

[30. Anticoagulants](#)

Jerrold H. Levy

[Heparin](#)

[Pharmacokinetics](#)

[Laboratory Evaluation of Coagulation](#)

[Activated Partial Thromboplastin Time and Anti-Factor Xa](#)

[Activated Clotting Time](#)

[Clinical Uses](#)

[Heparin-Induced Thrombocytopenia](#)

[Allergic Reactions](#)

[Reversal of Heparin-Induced Anticoagulation With Protamine](#)

[Low-Molecular-Weight Heparins](#)

[Spinal and Epidural Hematomas](#)

[Fondaparinux](#)

[Danaparoid](#)

[Prophylaxis Against Venous Thromboembolism](#)

[Direct Thrombin Inhibitors: Parenteral Agents](#)

[Bivalirudin](#)

[Argatroban](#)

[Lepirudin and Desirudin](#)

[Oral Anticoagulants](#)

[Vitamin K Antagonists—Warfarin](#)

[Mechanism of Action](#)

[Pharmacokinetics](#)

[Laboratory Evaluation](#)

[Clinical Uses](#)

[Management Before Elective Surgery](#)

[Direct-Acting Non-vitamin K Oral Anticoagulants](#)

[Direct Factor Xa Inhibitors](#)

Direct Thrombin Inhibitors
Perioperative Management of the Direct-Acting Non-vitamin K Oral Anticoagulants
Platelet Inhibitors
Aspirin
Thienopyridines: Clopidogrel, Prasugrel, and Ticagrelor
Cangrelor
Dipyridamole
Dextran
Platelet Glycoprotein IIb/IIIa Antagonists
Perioperative Management of Patients on Platelet Inhibitors
Thrombolytic Drugs
31. Physiology and Management of Massive Transfusion
Jerrold H. Levy
Pathophysiology of Hemostatic Abnormalities Associated With Trauma
Trauma and Endothelial Dysfunction
Massive Transfusion
Therapeutic Approaches for Massive Transfusion and Coagulopathy
Adverse Effects of Transfusions
Hemostatic Changes Associated With Massive Transfusion Coagulopathy
Perioperative Hemostatic Changes
Massive Transfusion Coagulopathy
Role of Red Blood Cells and Anemia
Causes of Bleeding in the Setting of Massive Transfusion Coagulopathy
Hypothermia, Acidosis, and Coagulopathy
Dilutional Coagulopathy
Fibrinolysis
Hypofibrinogenemia
Monitoring Hemostasis During Massive Transfusion
Treatment of Coagulopathy During Massive Transfusion
Plasma/Fresh Frozen Plasma
Platelet Administration
Antifibrinolytic Agents
Procoagulants
Goal-Directed Management
Postpartum Hemorrhage
Multimodal Resuscitation: Damage Control Resuscitation
Summary.

PART VI

Gastrointestinal System and Metabolism

32. Gastrointestinal Physiology

Michael J. Murray

Liver

Anatomy

Hepatic Blood Flow

Control of Hepatic Blood Flow

Reservoir Function

Bile Secretion

Bile Salts

Bilirubin

Cholesterol

[Metabolic Functions](#)
[Carbohydrates](#)
[Lipids](#)
[Proteins](#)
[Gastrointestinal Tract](#)
[Anatomy](#)
[Blood Flow](#)
[Portal Venous Pressure](#)
[Splenic Circulation](#)
[Innervation](#)
[Motility](#)
[Ileus](#)
[Salivary Glands](#)
[Esophagus](#)
[Lower Esophageal Sphincter](#)
[Gastroesophageal Reflux Disease](#)
[Hiatal Hernia](#)
[Achalasia](#)
[Stomach](#)
[Gastric Secretions](#)
[Parietal Cells](#)
[Chief Cells](#)
[G Cells](#)
[Gastric Fluid Volume and Rate of Gastric Emptying](#)
[Gastric Emptying Prior to Elective Surgery](#)
[Opioid-Induced Slowing of Gastric Emptying](#)
[Measurement of the Rate of Gastric Emptying](#)
[Vomiting](#)
[Small Intestine](#)
[Secretions of the Small Intestine](#)
[Absorption From the Small Intestine](#)
[Colon](#)
[Secretions of the Colon](#)
[Pancreas](#)
[Regulation of Pancreatic Secretions](#)
[33. Metabolism](#)
Michael J. Murray
[Carbohydrate Metabolism](#)
[Glycogen](#)
[Gluconeogenesis](#)
[Energy Release From Glucose](#)
[Anaerobic Glycolysis](#)
[Lipid Metabolism](#)
[Protein Metabolism](#)
[Storage of Amino Acids](#)
[Plasma Proteins](#)
[Albumin](#)
[Coagulation Factors](#)
[Use of Proteins for Energy](#)
[Effects of Stress on Metabolism](#)
[Obesity](#)

Pharmacologic Treatment

34. Antiemetics

Christopher M. Lam • Michael J. Murray

Definition

Incidence

Pathophysiology

Prophylaxis

Patient Factors

Surgical Factors

Anesthetic Factors

Pharmacologic Interventions

5-HT₃ Receptor Antagonists

Clinical Uses

Comparison With Other Antiemetics

Pharmacokinetics

Anticholinergics

Scopolamine

Central Anticholinergic Syndrome

Overdose

Decreased Barrier Pressure

Histamine Receptor Antagonists

Corticosteroids

Dopamine Receptor Antagonists

Benzamides

Butyrophenones

Neurokinin-1 Antagonists

Midazolam

Cannabinoids

Summary

35. Antacids and Gastrointestinal Motility Drugs

Michael J. Murray

Oral Antacids

Complications of Antacid Therapy

Drug Interactions

Histamine-Receptor Antagonists

H₁-Receptor Antagonists

Pharmacokinetics

Clinical Uses

Side Effects

H₂-Receptor Antagonists

Mechanism of Action

Pharmacokinetics

Clinical Uses

Side Effects

Drug Interactions

Proton Pump Inhibitors

Choice of PPI

Omeprazole

Esomeprazole

Pantoprazole

Gastrointestinal Prokinetics

[Dopamine Blockers](#)
[Domperidone](#)
[Metoclopramide](#)
[Macrolides](#)
[5-HT₄-Receptor Agonists](#)
[Serotonin Agonists](#)
[36. Nutrition](#)
Michael J. Murray
[Definitions](#)
[Malnutrition](#)
[Nutrition Support](#)
[Enteral Nutrition](#)
[Enteral Tube Feeding](#)
[Side Effects](#)
[Parenteral Nutrition](#)
[Short-Term Parenteral Therapy](#)
[Long-Term Total Parenteral Nutrition](#)
[Side Effects](#)
[Monitoring During TPN](#)
[Preparation of TPN Solutions](#)
[Immunonutrition](#)
[Vitamins, Dietary Supplements, and Herbal Remedies](#)
[Vitamins](#)
[Water-Soluble Vitamins](#)
[Fat-Soluble Vitamins](#)
[Dietary Supplements](#)
[Adverse Effects and Drug Interactions](#)

PART VII

Endocrine System

[37. Normal Endocrine Function](#)
Priya Patidar • Vivek K. Moitra
[Mechanism of Hormone Action](#)
[Hypothalamus and Pituitary Gland](#)
[Anterior Pituitary](#)
[Growth Hormone \(Somatotropin\)](#)
[Prolactin](#)
[Gonadotropins](#)
[Adrenocorticotrophic Hormone](#)
[Thyroid-Stimulating Hormone](#)
[Posterior Pituitary](#)
[Arginine Vasopressin](#)
[Oxytocin](#)
[Thyroid Gland](#)
[Mechanism of Action](#)
[Calcitonin](#)
[Parathyroid Glands](#)
[Adrenal Cortex](#)
[Mineralocorticoids: Aldosterone](#)
[Physiologic Effects](#)
[Mechanism of Action](#)

[Regulation of Secretion](#)
[Glucocorticoids: Cortisol](#)
[Physiologic Effects](#)
[Mechanism of Action](#)
[Regulation of Secretion](#)
[Effect of Anesthesia and Surgery](#)

[Reproductive Glands](#)
[Testes](#)
[Ovaries](#)
[Estrogens](#)
[Progesterone](#)
[Menstruation](#)
[Pregnancy](#)
[Menopause](#)
[Pancreas](#)
[Insulin](#)
[Regulation of Secretion](#)
[Physiologic Effects](#)

[Glucagon](#)
[Somatostatin](#)
[Pancreatic Polypeptide](#)

[38. Drugs that Alter Glucose Regulation](#)

Bianca Bromberger • Vivek K. Moitra

[Diabetes Mellitus](#)
[Insulin](#)
[Pharmacokinetics](#)
[Insulin Preparations and Delivery](#)

[Lispro](#)
[Insulin Aspart and Glulisine](#)
[Regular Insulin \(Crystalline Zinc Insulin\)](#)
[Neutral Protamine Hagedorn](#)
[Glargine, Detemir, and Degludec](#)

[Side Effects](#)
[Hypoglycemia](#)
[Allergic Reactions](#)
[Lipodystrophy](#)

[Insulin Resistance](#)
[Drug Interactions](#)
[Other Glucose Regulators](#)

[Metformin](#)
[Pharmacokinetics](#)
[Mechanism of Action](#)

[Side Effects](#)
[Sulfonylureas](#)
[Mechanism of Action](#)

[Pharmacokinetics](#)
[Side Effects](#)
[Glyburide](#)
[Glipizide](#)
[Glimepiride](#)

[Thiazolidinediones](#)

[Glucagon-like Peptide-1 Receptor Agonists](#)

[Side Effects](#)

[Pharmacokinetics](#)

[Sodium-Glucose Cotransporter 2 Inhibitors](#)

[Side Effects](#)

[Dipeptidyl-Peptidase-4 Inhibitors](#)

[Other Medications](#)

[Combination Therapy](#)

[39. Drugs for the Treatment of Hypothyroidism and Hyperthyroidism](#)

Dasun Peramunage • Vivek K. Moitra

[Hypothyroidism](#)

[Synthetic Thyroxine \(Levothyroxine\)](#)

[Triiodothyronine Formulations \(Liothyronine\)](#)

[Hyperthyroidism](#)

[Thionamides \(Methimazole, Propylthiouracil, Carbimazole\)](#)

[Side Effects](#)

[Iodine \(Saturated Potassium Iodide Solutions, Potassium Iodide-Iodine \[Lugol Solution\]\)](#)

[Radioactive Iodine](#)

[Thyroid Storm](#)

[40. Other Endocrine Drugs](#)

Artem Emple • Vivek K. Moitra

[Corticosteroids](#)

[Structure-Activity Relationships](#)

[Mechanism of Action](#)

[Maintenance of Homeostasis](#)

[Permissive Actions](#)

[Protective Actions](#)

[Pharmacokinetics](#)

[Synthetic Corticosteroids](#)

[Prednisolone](#)

[Prednisone](#)

[Methylprednisolone](#)

[Betamethasone](#)

[Dexamethasone](#)

[Triamcinolone](#)

[Clinical Uses](#)

[Deficiency States](#)

[Allergic Therapy](#)

[Asthma](#)

[Antiemetic Effect](#)

[Postoperative Analgesia](#)

[Cerebral Edema](#)

[Aspiration Pneumonitis](#)

[Lumbar Disc Disease](#)

[Immunosuppression](#)

[Arthritis](#)

[Collagen Diseases](#)

[Ocular Inflammation](#)

[Cutaneous Disorders](#)

[Postintubation Laryngeal Edema](#)

[Ulcerative Colitis](#)

[Myasthenia Gravis](#)
[Respiratory Distress Syndrome](#)
[Leukemia](#)
[Cardiac Arrest](#)
[Septic Shock](#)
[Side Effects](#)
[Corticosteroid Supplementation in the Perioperative Period](#)
[Electrolyte and Metabolic Changes and Weight Gain](#)
[Osteoporosis](#)
[Peptic Ulcer Disease](#)
[Skeletal Muscle Myopathy](#)
[Central Nervous System Dysfunction](#)
[Peripheral Blood Changes](#)
[Inhibition of Normal Growth](#)
[Inhibitors of Corticosteroid Synthesis](#)
[Metyrapone](#)
[Mitotane](#)
[Drugs That Regulate Calcium](#)
[Hypercalcemia](#)
[Bisphosphonates](#)
[Glucocorticoids](#)
[Hypocalcemia](#)
[Drugs for Pituitary Function](#)
[Anterior Pituitary Hormones](#)
[Growth Hormone](#)
[Gonadotropins](#)
[Adrenocorticotrophic Hormone](#)
[Melatonin](#)
[Posterior Pituitary Hormones](#)
[Arginine Vasopressin](#)
[Diabetes Insipidus](#)
[Hypotension During Anesthesia](#)
[Septic Shock](#)
[Refractory Cardiac Arrest](#)
[Esophageal Varices](#)
[Side Effects](#)
[Oxytocin](#)
[Side Effects](#)
[Drugs for Reproductive Regulation](#)
[Ovarian Hormones](#)
[Estrogens](#)
[Antiestrogens](#)
[Tissue-Specific Estrogens](#)
[Progesterone](#)
[Antiprogestins](#)
[Oral Contraceptives](#)
[Androgens](#)
[Route of Administration](#)
[Side Effects](#)
[Danazol](#)
[Finasteride](#)

PART VIII

Miscellaneous

41. Antimicrobials, Antiseptics, Disinfectants, and Management of Perioperative Infection

Stephanie J. Pan • Pamela Flood

Introduction

Antimicrobial Prophylaxis for Surgical Procedures

Antimicrobial Selection

Nosocomial Infections

Special Patient Groups

Parturients

Elderly Patients

Human Immunodeficiency Virus-Infected Patients

Antibacterial Drugs Commonly Used in the Perioperative Period

Penicillins

Clinical Indications

Excretion

Duration of Action

Penicillinase-Resistant Penicillins

Penicillinase-Susceptible Broad-Spectrum Penicillins (Second-Generation Penicillins).

Ampicillin

Amoxicillin

Extended-Spectrum Carboxypenicillins (Third-Generation Penicillins).

Carbenicillin

Extended-Spectrum Acylaminopenicillins (Fourth-Generation Penicillins).

Penicillin β -Lactamase Inhibitor Combinations

Cephalosporins

Cephalosporins and Allergy to Penicillins

Cross-reactivity

Classification

Other β -Lactam Antimicrobials

Aztreonam

Aminoglycoside Antimicrobials

Side Effects

Macrolides

Erythromycin

Azithromycin

Clindamycin

Side Effects

Vancomycin

Side Effects

Linezolid

Side Effects

Bacitracins

Metronidazole

Fluoroquinolones

Ciprofloxacin

Moxifloxacin

Antiseptic and Disinfectant Prophylaxis for Surgical Procedures

Topical Antiseptics

Alcohols

Chlorhexidine

[Iodine](#)

[Quaternary Ammonium Compounds](#)

[Hexachlorophene](#)

[Methods for Sterilization of Instruments](#)

[Formaldehyde](#)

[Glutaraldehyde](#)

[Pasteurization](#)

[Cresol](#)

[Silver Nitrate](#)

[Ethylene Oxide](#)

[42. Chemotherapeutic Drugs](#)

Ami K. Patel • Richard D. Urman • James P. Rathmell

[Drug Resistance](#)

[Classification](#)

[Toxicities](#)

[Alkylating Agents](#)

[Side Effects](#)

[Nitrogen Mustards](#)

[Mechlorethamine](#)

[Cyclophosphamide](#)

[Melphalan](#)

[Chlorambucil](#)

[Alkyl Sulfonates](#)

[Side Effects](#)

[Nitrosoureas](#)

[Carmustine](#)

[Lomustine and Semustine](#)

[Streptozocin](#)

[Mitomycin](#)

[Platinating Drugs](#)

[Cisplatin](#)

[Side Effects](#)

[Antimetabolites](#)

[Folate Analogues](#)

[Methotrexate](#)

[Pyrimidine Analogues](#)

[Fluorouracil](#)

[Capecitabine](#)

[Pemetrexed](#)

[Cytarabine](#)

[Gemcitabine](#)

[Purine Analogues](#)

[Mercaptopurine](#)

[Thioguanine](#)

[Pentostatin and Cladribine](#)

[Hydroxyurea](#)

[Topoisomerase Inhibitors](#)

[Doxorubicin and Daunorubicin](#)

[Clinical Uses](#)

[Side Effects](#)

[Dactinomycin](#)

[Clinical Uses](#)
[Side Effects](#)
[Bleomycin](#)
[Clinical Uses](#)
[Side Effects](#)
[Tubulin-Binding Drugs](#)
[Vinca Alkaloids](#)
[Side Effects](#)
[Taxanes](#)
[Side Effects](#)
[Estramustine](#)
[Signal Transduction Modulators](#)
[Progestins](#)

[Estrogens and Androgens](#)
[Antiestrogens](#)
[Antiandrogens](#)
[Aromatase Inhibitors](#)
[Monoclonal Antibodies](#)
[Other Targeted Therapies](#)
[Vaccines](#)

[Immunomodulatory Drugs](#)

[Cancer Immunotherapies](#)

[Adoptive Cellular Therapy](#)

[Chimeric Antigen Receptor T Cells](#)

[43. Psychopharmacologic Drugs](#)

Peter J. van Roessel • Carolyn Rodriguez • Pamela Flood

[Drugs With Primarily Serotonergic Activity](#)

[Mechanisms of Action](#)

[Serotonin Receptors](#)

[Serotonin Reuptake Inhibitors](#)

[Adverse Effects](#)

[Selective Serotonin Reuptake Inhibitors](#)

[Serotonin-Norepinephrine Reuptake Inhibitors](#)

[Tricyclic Serotonin Reuptake Inhibitors](#)

[Serotonin Multimodal Drugs](#)

[Serotonin Agonist](#)

[Serotonin and Norepinephrine Multimodal Drugs](#)

[Monoamine Oxidase Inhibitors](#)

[Monoamine Oxidase Enzyme System](#)

[Mechanisms of Action](#)

[Adverse Effects](#)

[Dietary Restrictions](#)

[Drug Interactions](#)

[Overdose](#)

[Management of Anesthesia](#)

[Drugs With Primarily Noradrenergic Activity](#)

[Tricyclic and Related Antidepressants](#)

[Mechanisms of Action](#)

[Utility in Chronic Pain Syndromes](#)

[Adverse Effects](#)

[Tolerance](#)

[Pharmacokinetics](#)

[Drug Interactions](#)

[Overdose](#)

[Other Norepinephrine Reuptake Inhibitor Drugs](#)

[Norepinephrine Agonists](#)

[Norepinephrine Dopamine Reuptake Inhibitor](#)

[Drugs With Primarily Dopaminergic Activity](#)

[Dopamine Norepinephrine Multimodal Drugs](#)

[Dopamine Reuptake Inhibitor Drugs](#)

[Dopamine Agonists](#)

[Dopamine Antagonists](#)

[Mechanisms of Action](#)

[First-Generation Antipsychotics](#)

[Antiemetic Effects](#)

[Adverse Effects](#)

[Drug Interactions](#)

[Dopamine and Serotonin Antagonist Drugs](#)

[Clozapine](#)

[Olanzapine](#)

[Risperidone, Paliperidone, and Iloperidone](#)

[Aripiprazole, Brexpiprazole, and Cariprazine](#)

[Ziprasidone and Lurasidone](#)

[Amisulpride](#)

[Long-Acting Injectable Formulations](#)

[Dopamine Serotonin Norepinephrine Multimodal Drugs](#)

[Drugs With Primarily Glutamatergic Activity](#)

[Glutamate Antagonists and Channel Blockers](#)

[Valproate, Carbamazepine, and Oxcarbazepine](#)

[Lamotrigine](#)

[Gabapentin and Pregabalin](#)

[Glutamate Antagonist Drugs](#)

[Other Glutamate Modulators](#)

[Drugs With Primarily Acetylcholinergic Action](#)

[Acetylcholinesterase Inhibitors](#)

[Anesthetic Considerations](#)

[Acetylcholine Receptor Agonist and Multimodal Drugs](#)

[Drugs With Primarily \$\gamma\$ -Aminobutyric Acid \(GABA\)-ergic Action](#)

[Benzodiazepines](#)

[Other GABA_A Receptor Modulators](#)

[Lithium](#)

[Mechanisms of Action](#)

[Dosage and Monitoring](#)

[Adverse Effects](#)

[Renal Effects](#)

[Cardiac Effects](#)

[Endocrine Effects](#)

[Drug Interactions](#)

[Anesthetic Considerations](#)

[Toxicity](#)

[Cannabinoids](#)

[Pharmacokinetics](#)

[Toxicity](#)
[Clinical Uses](#)
[Conclusion](#)

PART IX

Special Populations

[44. Physiology of the Newborn](#)

Becky J. Wong • Lisa Wise-Faberowski

[Neonatal Physiology](#)

[Neonatal Cardiovascular Physiology](#)

[Respiratory Physiology of the Newborn](#)

[Neonatal Thermoregulation](#)

[Neonatal Fluid, Electrolyte, and Renal Physiology](#)

[Neonatal Neurophysiology](#)

[Neonatal Hepatic Physiology](#)

[45. Maternal and Fetal Physiology and Pharmacology](#)

Amy W. Willett • Pamela Flood

[Introduction](#)

[Maternal Physiology](#)

[Physiologic Changes During Pregnancy and Delivery](#)

[Cardiovascular Changes](#)

[Intravascular Volumes and Hematology](#)

[Cardiac Output](#)

[Systemic Vascular Resistance](#)

[Aortocaval Compression](#)

[Pulmonary Changes](#)

[Airway](#)

[Minute Ventilation and Oxygenation](#)

[Lung Volumes](#)

[Gastrointestinal Changes](#)

[Renal Changes](#)

[Neurologic Changes](#)

[Uteroplacental Physiology](#)

[Uterine Blood Flow](#)

[Oxygen Transfer](#)

[Principles of Nonobstetric Surgery During Pregnancy](#)

[Fetal Heart Rate Monitoring](#)

[Intraoperative Considerations for Nonobstetric Surgery](#)

[Postoperative Pain Management](#)

[Fetal Physiology](#)

[Characteristics of the Fetal Circulation](#)

[Drug Transfer](#)

[Fetal Liver Function and Drug Metabolism](#)

[Anesthetic Toxicity in the Fetus](#)

[Fetal Neurophysiology](#)

[Fetal Pain](#)

[46. Physiology and Pharmacology of the Elderly](#)

Andrea Girnius • Pamela Flood

[Aging and the Cardiovascular System](#)

[Heart](#)

[Large Vessels](#)

[Endothelial Function](#)
[Conduction System](#)
[Autonomic and Integrated Cardiovascular Responses](#)
[Anesthetic and Ischemic Preconditioning in the Aging Heart](#)
[Aging and the Respiratory System](#)
[Respiratory System Mechanics and Architecture](#)
[Lung Volumes and Capacities](#)
[Vital Capacity](#)
[Residual Volume](#)
[Total Lung Capacity](#)
[Functional Residual Capacity](#)
[Closing Capacity](#)
[Expiratory Flow](#)
[Diffusing Capacity and Alveolar-to-Arterial Oxygen Gradient](#)
[Upper Airway Protective Reflexes](#)
[Control of Breathing, Chemoreceptors, and Integrated Responses](#)
[Sleep-Disordered Breathing](#)
[The Coagulation System in the Elderly](#)
[Thermoregulation in the Elderly](#)
[Resting Core Temperature](#)
[Response to Cold Stress](#)
[Gastrointestinal Function in the Elderly](#)
[Liver](#)
[Gastroesophageal Physiology](#)
[Renal Function in the Elderly](#)
[Skeletal Muscle Mass and Aging](#)
[Neurophysiology of Aging](#)
[Pain and Aging](#)
[Conclusion](#)
[47. Physiology and Pharmacology of Resuscitation](#)
Michael J. Murray • Sean M. Dennig
[Pathophysiology](#)
[Cardiac Arrest](#)
[Hemorrhagic Shock](#)
[Pulmonary Arrest](#)
[Pharmacology](#)
[Cardiopulmonary Resuscitation](#)
[Epinephrine](#)
[Amiodarone](#)
[Hemorrhage](#)
[Tranexamic Acid](#)
[Oxygenation/Ventilation](#)

[Drug Index](#)

[Subject Index](#)

PART I Basic Principles of Physiology and Pharmacology

Basic Principles of Physiology

Pamela Flood • Lisa Wise-Faberowski • Steven L. Shafer

This chapter reviews the basic principles of the composition of the body, and the structure of cells. Although very basic, these principles are essential for everything that follows.

Body Composition

Water is the medium in which all metabolic reactions occur. Water accounts for about 60% of the weight in an adult man and about 50% of the body weight in an adult woman ([Figure 1.1](#)).¹ In a neonate, total body water may represent 70% of body weight. Total body water is less in women and obese individuals, reflecting the decreased water content of adipose tissue. Advanced age is also associated with increased fat content and decreased total body water ([Table 1.1](#)). Body fluids can be divided into intracellular and extracellular fluid depending on their location relative to the cell membrane (see [Figure 1.1](#)).¹ Approximately two-thirds of the total body fluid in an adult are contained inside the estimated 100 trillion cells of the body. The fluid in these cells, despite individual differences in constituents, is collectively designated *intracellular fluid*. *Extracellular fluid*, one-third of fluid outside the cells, is divided into interstitial fluid and plasma (intravascular fluid) by the capillary membrane (see [Figure 1.1](#)).¹

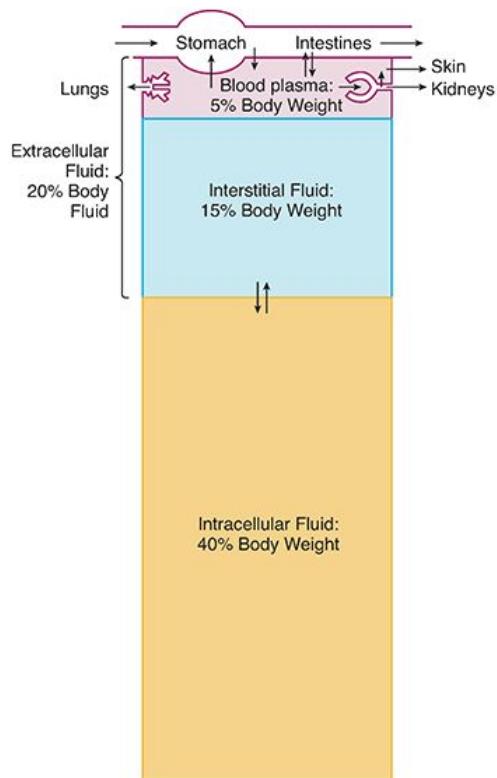


FIGURE 1.1 Body fluid compartments and the percentage of body weight represented by each compartment. The location relative to the capillary membrane divides extracellular fluid into plasma or interstitial fluid. Arrows represent fluid movement between compartments. *Reprinted with permission from Gamble JL. Chemical Anatomy, Physiology, and Pathology of Extracellular Fluid: A Lecture Syllabus. 6th*

ed. Cambridge, MA: Harvard University Press; 1954:9. Copyright © 1954 by the President and Fellows of Harvard College.

TABLE 1.1

Total body water by age and gender

Age (y)	Total body water	
	Men (%)	Women (%)
18-40	61	51
41-60	55	47
>60	52	46

Interstitial fluid is present in the spaces between cells. An estimated 99% of this fluid is held in the gel structure of the interstitial space. Plasma is the noncellular portion of blood. The average plasma volume is 3 L, a little over half of the blood volume of 5 L. Plasma is in dynamic equilibrium with the interstitial fluid through pores in the capillaries, the interstitial fluid serving as a reservoir from which water and electrolytes can be mobilized into the circulation. Loss of plasma volume from the intravascular space is minimized by colloid osmotic pressure exerted by the plasma proteins.

Other extracellular fluid that may be considered as part of the interstitial fluid includes cerebrospinal fluid, gastrointestinal fluid (because it is mostly resorbed), and fluid in potential spaces (pleural space, pericardial space, peritoneal cavity, synovial cavities). Excess amounts of fluid in the interstitial space manifest as peripheral edema.

The normal daily intake of water (drink and internal product of food metabolism) by an adult averages 2.5 L, of which about 1.5 L is excreted as urine, 100 mL is lost in sweat, and 100 mL is present in feces. Insensible water losses occur with respiration and diffusion through the skin. Inhaled air, saturated with water vapor (47 mm Hg at 37°C), is subsequently exhaled, accounting for an average daily water loss through the lungs of 300 to 400 mL. The water content of inhaled air decreases with decreases in ambient air temperature such that more endogenous water is required to achieve a saturated water vapor pressure at body temperature. As a result, insensible water loss from the lungs is greatest in cold environments and least in warm temperatures. The remaining 400 mL of insensible losses is by diffusion through the skin and is not perceived as sweat. Insensible water loss is limited by the mostly impermeable cornified layer of the skin. When the cornified layer is removed or interrupted, as after burn injury, the loss of water through the skin is greatly increased.

Blood Volume

Blood contains extracellular fluid, the plasma, and intracellular fluid, mostly held in erythrocytes. The body has multiple systems to maintain intravascular fluid volume, including renin-angiotensin system, and arginine vasopressin (antidiuretic hormone), that increase fluid resorption in the kidney and evoke changes in the renal tubules that lead to restoration of intravascular fluid volume (see [Chapter 16](#)).

The average blood volume of an adult is 5 L, compromising about 3 L of plasma and 2 L of erythrocytes. These volumes vary with age, weight, and gender. For example, in nonobese individuals, the blood volume varies in direct proportion to the body weight, averaging 70 mL/kg for lean men and women. The greater the ratio of fat to body weight, however, the less is the blood volume in milliliter per kilogram because adipose tissue has a decreased vascular supply. The hematocrit or packed cell volume is approximately the erythrocyte fraction blood. The normal hematocrit is about 45% for men and postmenopausal women and about 38% for menstruating women, with a range of approximately ±5%.

Constituents of Body Fluid Compartments

The constituents of intracellular and extracellular fluid are identical, but the quantity of each substance varies among the compartments ([Figure 1.2](#)).² The most striking differences are the low protein content in interstitial fluid compared with intracellular fluid and plasma and the fact that sodium and chloride ions are

largely extracellular, whereas most of the potassium ions (approximately 90%) are intracellular. This unequal distribution of ions results in establishment of a potential (voltage) difference across cell membranes.

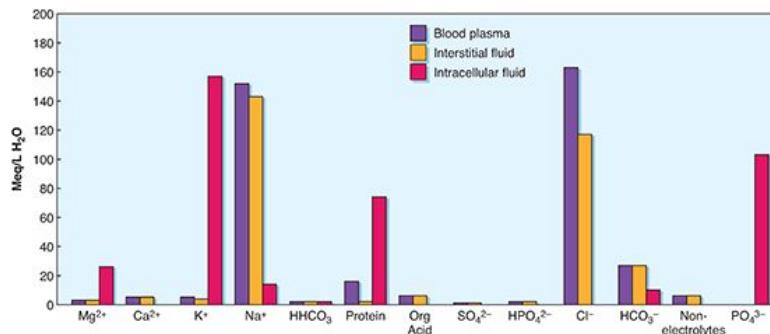


FIGURE 1.2 Electrolyte composition of body fluid compartments.

The constituents of extracellular fluid are carefully regulated by the kidneys so that cells are bathed in an osmotically neutral fluid containing the proper concentrations of electrolytes and nutrients. The normal amount of sodium and potassium in the body is about 58 mEq/kg and 45 mEq/kg, respectively. Trauma is associated with progressive loss of potassium through the kidneys. For example, a patient undergoing surgery excretes about 100 mEq of potassium in the first 48 hours postoperatively and, after this period, about 25 mEq daily. Plasma potassium concentrations are not good indicators of total body potassium content because most potassium is intracellular. There is a correlation, however, between the potassium and hydrogen ion content of plasma, the two increasing and decreasing together. In metabolic acidosis, there is net efflux of potassium out of the cells to compensate for the hydrogen ion influx and preserve the resting potential. As metabolic acidosis is treated, the plasma potassium will fall from that measured in the acidotic state.

Osmosis

Osmosis is the movement of water (solvent molecules) across a semipermeable membrane from a compartment in which the nondiffusible solute (ion) concentration is lower to a compartment in which the solute concentration is higher ([Figure 1.3](#)).³ The lipid bilayer that surrounds all cells is freely permeable to water but is impermeable to ions. As a result, water rapidly moves across the cell membrane to establish osmotic equilibration, which happens almost instantly.

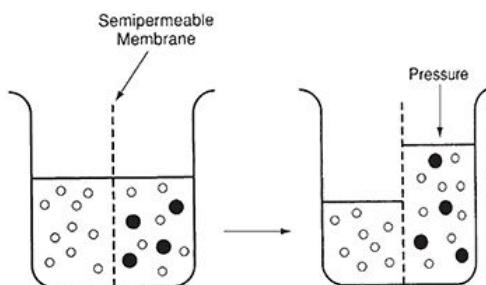


FIGURE 1.3 Diagrammatic representation of osmosis depicting water molecules (open circles) and solute molecules (solid circles) separated by a semipermeable membrane. Water molecules move across the semipermeable membrane to the area of higher concentration of solute molecules. Osmotic pressure is the pressure that would have to be applied to prevent continued movement of water molecules. *Republished with permission of McGraw Hill LLC from Ganong WF. Review of Medical Physiology. 21st ed. New York, NY: Lange Medical Books/McGraw-Hill; 2003; permission conveyed through Copyright Clearance Center, Inc.*

Cells control their size by controlling intracellular osmotic pressure. The maintenance of a normal cell volume and pressure depends on sodium-potassium adenosine triphosphatase (ATPase) (sodium-potassium exchange pump), which maintains the intracellular-extracellular ionic balance by removing three sodium ions

from the cell for every two potassium ions brought into the cell. The sodium-potassium pump also maintains the transmembrane electrical potential and the sodium and potassium concentration gradients that power many cellular processes, including neuronal conduction.

The osmotic pressure exerted by nondiffusible particles in a solution is determined by the number of particles in the solution (with each ion counting as 1 unit) and not the type of particles (molecular weight) (see [Figure 1.3](#)).³ Thus, a 1-mol solution of glucose or albumin and 0.5-mol solution of sodium chloride exert the same osmotic pressure because the sodium chloride exists as independent sodium and chloride ions, each having a concentration of 0.5 mol.

Osmole is the unit used to express osmotic pressure in solutes, but the denominator for osmolality is kilogram of water. *Osmolarity* is the correct terminology when osmole concentrations are expressed in liters of body fluid (eg, plasma) rather than kilograms of water. Because it is much easier to express body fluids in liters of fluid rather than kilograms of free water, almost all physiology calculations are based on osmolarity. Plasma osmolarity is important in evaluating dehydration, overhydration, and electrolyte abnormalities.

Normal plasma has an osmolarity of about 290 mOsm/L. All but about 20 mOsm of the 290 mOsm in each liter of plasma are contributed by sodium ions and their accompanying anions, principally chloride and bicarbonate. Proteins normally contribute <1 mOsm/L. The major nonelectrolytes of plasma are glucose and urea, and these substances can contribute significantly to plasma osmolarity when hyperglycemia or uremia is present, as suggested by the standard calculation of plasma osmolarity:

$$\text{Plasma osmolarity} = 2 (\text{Na}^+) + 0.055 (\text{glucose}) + 0.36 (\text{blood urea nitrogen}).$$

Tonicity of Fluids

Packed erythrocytes must be suspended in **isotonic** solutions to avoid damaging the cells ([Figure 1.4](#)).⁴ A 0.9% solution of sodium chloride is isotonic and remains so because there is no net movement of the osmotically active particles in the solution into cells, and the particles are not metabolized. A solution of 5% glucose in water is initially isotonic when infused, but glucose is metabolized, so the net effect is that of infusing a hypotonic solution. Lactated Ringer solution plus 5% glucose is initially hypertonic (about 560 mOsm/L), but as glucose is metabolized, the solution becomes less hypertonic.

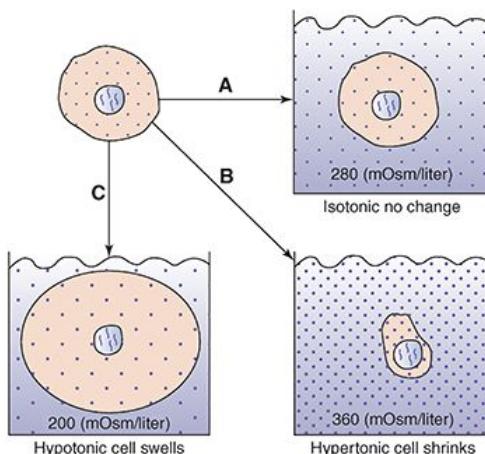


FIGURE 1.4 Effects of isotonic (A), hypertonic (B), and hypotonic (C) solutions on cell volume. Reprinted from Guyton AC, Hall JE. Textbook of Medical Physiology. 10th ed. Philadelphia, PA: W.B. Saunders; 2000. Copyright © 2000 Elsevier. With permission.

Fluid Management

The goal of fluid management is to maintain normovolemia characterized by hemodynamic stability. Crystalloids consist of water, electrolytes, and occasionally glucose that freely distribute along a concentration gradient between the two extracellular spaces. After 20 to 30 minutes, an estimated 75% to

80% of an isotonic saline or a lactate-containing solution will have distributed outside the confines of the circulation, thus limiting the efficacy of these solutions in treating hypovolemia. The major goal of fluid resuscitation is to maintain microcirculatory perfusion to preserve the delivery of oxygen and glucose to the tissues. Measurement of systemic blood pressure or central venous pressure does not provide an accurate picture of specific organ micro perfusion. Indeed, microperfusion of individual organs is tightly regulated in most situations to prioritize tissue perfusion to the brain with other organs delegated to secondary status. A variety of techniques have been developed to measure microcirculation, the most common being sublingual with handheld microscopy.⁵

Hypotonic intravenous fluids equilibrate with extracellular fluid, causing it to become hypotonic with respect to intracellular fluid. When this occurs, osmosis rapidly increases intracellular water, causing cellular swelling. Increased intracellular fluid volume is particularly undesirable in patients with increased intracranial pressure or an intracranial mass. Protection from excessive fluid accumulation in the interstitial compartment is mediated by lymphatic flow, which can increase as much as tenfold but can be overwhelmed. The lymphatic system can be obstructed by surgery as after extensive axillary resection for breast cancer and tumor invasion causing distal tissue edema.

Hypertonic saline solutions (7.5% sodium chloride) have been useful for rapid intravascular fluid repletion during resuscitation as during hemorrhagic and septic shock. Hypertonic saline solutions compare favorably with mannitol for lowering intracranial pressure.⁶ The primary effect of hypertonic saline solutions (increase systemic blood pressure and decrease intracranial pressure) most likely reflects increased intravascular fluid volume because of fluid shifts and movement of water away from uninjured region of the brain. In a secondary analysis of the data from the Resuscitation Outcomes Consortium Hypertonic Saline Trial Shock Study and Traumatic Brain Injury Study, the effect of hypertonic saline alone was compared with that of hypertonic saline plus mannitol on renal function after acute brain injury.⁷ The combination was not superior to treatment with hypertonic saline alone. The use of hypertonic saline solutions is viewed as short-term treatment as hypertonicity and hypernatremia are likely with sustained administration.

Albumin should remain within the intracellular space longer than crystalloids in the setting of an intact vascular endothelial and blood-brain barrier. However, the vascular endothelium is commonly damaged by trauma, hyperglycemia, and sepsis, obviating this advantage.⁸ While the administration of albumin makes sense, no randomized controlled trial has demonstrated long-term benefit over other solutions except perhaps in septic shock.⁹

Dehydration

Loss of water by gastrointestinal or renal routes or by diaphoresis is associated with an initial deficit in extracellular fluid volume. Intracellular water partly repletes this loss through osmosis, keeping the osmolarities in both compartments equal despite decreased absolute volume (dehydration) of both compartments. The ratio of extracellular fluid to intracellular fluid is greater in infants than adults, but the absolute volume of extracellular fluid is obviously less in infants. This is why dehydration develops more rapidly and is often more severe in the very young. Clinical signs of dehydration are likely when about 5% to 10% (severe dehydration) of total body water has been lost in a brief period of time. Physiologic mechanisms can usually compensate for acute loss of 15% to 25% of the intravascular fluid volume, whereas a greater loss places the patient at risk for hemodynamic decompensation.

Cell Structure and Function

The basic living unit of the body is the cell. It is estimated that the entire body consists of 38 trillion cells, 85% of which are (amazingly) erythrocytes. We cohabit our bodies with an approximately equal number of bacterial cells, which fortunately only contribute about 0.2 kg to our total mass.¹⁰ Each organ is a mass of cells held together by intracellular supporting structures.

All mammalian cells literally burn nutrients (ie, carbohydrates, lipids, proteins) using intracellular oxygen to release energy necessary for cellular function. Almost every cell is within 25 to 50 microns of a capillary, assuring prompt diffusion of oxygen to cells. All cells exist in nearly the same composition of

extracellular fluid. Our organs (lungs, kidneys, gastrointestinal tract) function to maintain a constant composition (homeostasis) of extracellular fluid.

Cell Anatomy

The principal components of cells include the nucleus (except for mature red blood cells) and the cytoplasm, which contains structures known as *organelles* (Figure 1.5).¹¹ The nucleus is separated from the cytoplasm by the nuclear membrane, and the cytoplasm is separated from surrounding fluids by a cell membrane. Organelles are also enclosed by membranes. All cellular membranes are lipid bilayers.

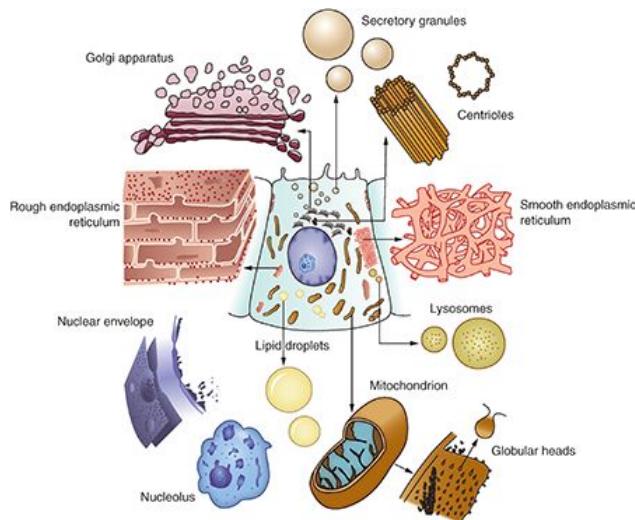


FIGURE 1.5 Schematic diagram of a hypothetical cell (center) and its organelles. Republished with permission of McGraw Hill LLC from Junqueira LC, Carneiro J, Kelley RO. Basic Histology. 7th ed. Norwalk, CT: Appleton & Lange, 1992; permission conveyed through Copyright Clearance Center, Inc.

Cell Membrane

The lipid bilayer acts as a permeability barrier, allowing the cell to maintain a cytoplasmic composition different from extracellular fluid. Proteins and phospholipids are the most abundant constituents of cell membranes (Table 1.2). The lipid bilayer is interspersed with large globular proteins (Figure 1.6).¹² Lipid bilayers are readily permeable to water, both through passive diffusion and through aquaporins, specialized proteins in the membrane that function as water channels described in the following text. Lipid bilayers are nearly impermeable to water-soluble substances, such as ions and glucose. Ions and charged water-soluble molecules require specialized channel and transport pumps to enter the intracellular environments. Conversely, fat-soluble substances (eg, steroids) and gases readily cross hydrophobic cell membranes.

TABLE 1.2	
Cell membrane composition	
Phospholipids	Lecithins (phosphatidylcholines) Sphingomyelins Amino phospholipids (phosphatidylethanolamine)
Proteins	Structural proteins (microtubules) Transport proteins (sodium-potassium ATPase) Ion channels Receptors Enzymes (adenylate cyclase)

Abbreviation: ATPase, adenosine triphosphatase.

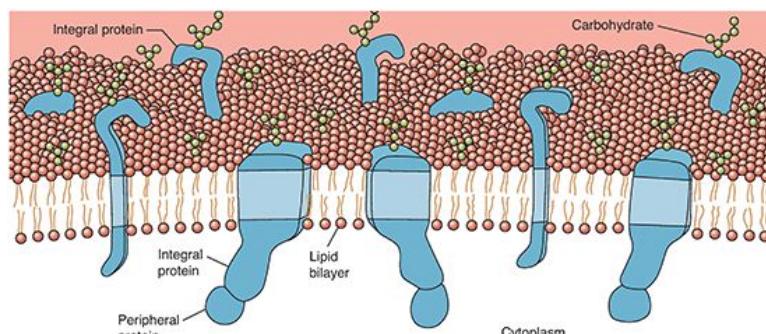


FIGURE 1.6 The cell membrane is a two molecule-thick lipid bilayer containing protein molecules that extend through the bilayer.

There are several types of proteins in the cell membrane (see [Table 1.2](#)). In addition to structural proteins (microtubules), there are transport proteins (eg, sodium-potassium ATPase) that function as pumps, actively transporting ions across cell membranes. Other proteins function as passive channels for ions that can be opened or closed by changes in the conformation of the protein. There are proteins that function as receptors to bind ligands (hormones or neurotransmitters), thus initiating physiologic changes inside cells. Another group of proteins function as enzymes (adenylate cyclase), catalyzing reactions at the surface of cell membranes. The protein structure of cell membranes, especially the enzyme content, varies from cell to cell.

Transfer of Molecules Through Cell Membranes

Diffusion

Oxygen, carbon dioxide, and nitrogen move through cell membranes by diffusion through the lipid bilayer. Because diffusion is relatively slow over macroscopic distances, organisms have developed circulatory systems to deliver nutrients within reasonable diffusion ranges of cells ([Table 1.3](#)). Water is also able to diffuse through cells as described earlier, although not as freely as the gases.

TABLE 1.3
Predicted relationship between diffusion distance and time

Diffusion distance (mm)	Time required for diffusion
0.001	0.5 ms
0.01	50 ms
0.1	5 s
1	498 s
10	14 h

Poorly lipid-soluble substances, such as glucose and amino acids, may pass through lipid bilayers by facilitated diffusion. For example, glucose combines with a carrier to form a complex that is lipid soluble. This lipid-soluble complex can diffuse to the interior of the cell membrane where glucose is released into the cytoplasm. The carrier then moves back to the exterior of the cell membrane, where it becomes available to transport more glucose from the extracellular fluid ([Figure 1.7](#)).⁴ As such, the carrier renders glucose soluble in cell membranes that otherwise would prevent its passage. Insulin greatly speeds facilitated diffusion of glucose and some amino acids across cell membranes.

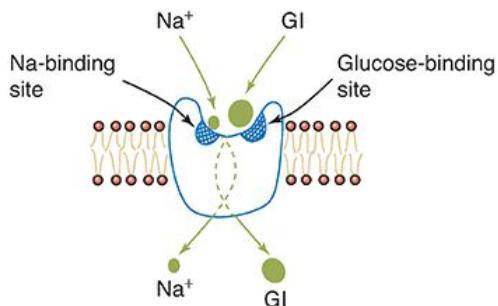


FIGURE 1.7 Glucose (Gl) can combine with a sodium (Na) cotransport carrier system at the outside surface of the cell membrane to facilitate diffusion (carrier-mediated diffusion) of Gl across the cell membrane. At the inside surface of the cell membrane, Gl is released to the interior of the cell and the carrier again becomes available for reuse. *Reprinted from Guyton AC, Hall JE. Textbook of Medical Physiology. 10th ed. Philadelphia, PA: W.B. Saunders; 2000. Copyright © 2000 Elsevier. With permission.*

Endocytosis and Exocytosis

Endocytosis and exocytosis transfer molecules such as nutrients across cell membranes without the molecule actually passing through a cell membranes. The uptake of particulate matter (bacteria, damaged cells) by cells is phagocytosis, whereas uptake of materials in solution in the extracellular fluid is pinocytosis ([Figure 1.8](#)).¹³ The process of phagocytosis is initiated when antibodies attach to damaged tissue and foreign substances (opsonization), facilitating binding to specialized proteins on the cell surface. Fusion of phagocytic or pinocytic vesicles with lysosomes allows intracellular digestion of materials to proceed. Neurotransmitters are ejected from cells by exocytosis from specialized presynaptic vesicles activated by an action potential. This process requires calcium ions and resembles endocytosis in reverse.

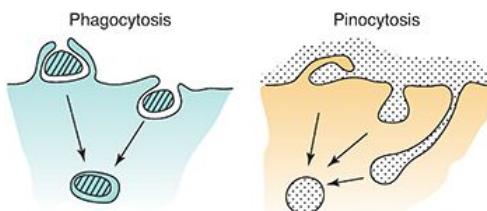


FIGURE 1.8 Schematic depiction of phagocytosis (ingestion of solid particles) and pinocytosis (ingestion of dissolved particles). *From Berne RM, Levy MN, Koeppen BM, et al. Physiology. 5th ed. St Louis, MO: Mosby; 2004. Reprinted with permission from Bruce M. Koeppen, MD.*

Sodium-Potassium Adenosine Triphosphatase

As mentioned previously, sodium-potassium ATPase, also known as the sodium-potassium pump, is an adenosine triphosphate (ATP)-dependent sodium and potassium transporter on the cell membrane that ejects three sodium ions from the cell in exchange for the import of two potassium ions ([Figure 1.9](#)).⁴ This action maintains oncotic equilibration across the cell membrane, reducing the number of intracellular ions to balance the large number of protein and other intracellular constituents. It also is responsible for creating the transmembrane electrical potential, creating a net positive charge on the outside of the cell from the excess of positive sodium ions outside compared to number of positive potassium ions inside of the cell. Lastly, it creates the sodium gradients responsible for propagation of the action potential and the potassium gradient that rapidly restores the resting membrane potential after conduction of an action potential. In the brain, the sodium-potassium pump accounts for nearly 50% of energy consumption.¹⁴

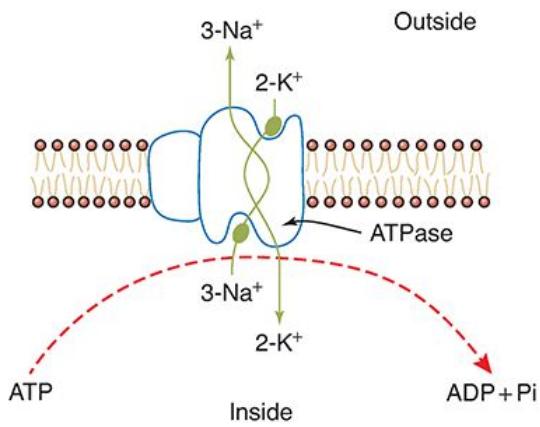


FIGURE 1.9 Sodium (Na)-potassium (K) adenosine triphosphatase (ATPase) is an enzyme present in all cells that catalyzes the conversion of adenosine triphosphate (ATP) to adenosine diphosphate (ADP). The resulting energy is used by the active transport carrier system (sodium pump) that is responsible for the outward movement of three sodium ions across the cell membrane for every two potassium ions that pass inward. Abbreviation: Pi, inorganic phosphate. *Reprinted from Guyton AC, Hall JE. Textbook of Medical Physiology. 10th ed. Philadelphia, PA: W.B. Saunders; 2000. Copyright © 2000 Elsevier. With permission.*

Other ion transporters include hydrogen-potassium ATPases in the gastric mucosa and renal tubules, the transporter that exchanges protons for potassium ions. Calcium ATPases are responsible for maintaining very low cytoplasmic concentrations of calcium, either by ejecting it from the cell (plasma membrane calcium ATPase) or sequestering calcium in the endoplasmic reticulum via the sarcoplasmic/endoplasmic reticulum calcium ATPase.¹⁵

Ion Channels

Ion channels are transmembrane proteins that generate electrical signals the brain, nerves, heart, and skeletal muscles (**Figure 1.10**).¹⁶ Ion channels use the energy stored in the chemical and electrical gradients created by sodium-potassium ATPase to rapidly initiate changes in transmembrane potential, causing conduction of an action potential.

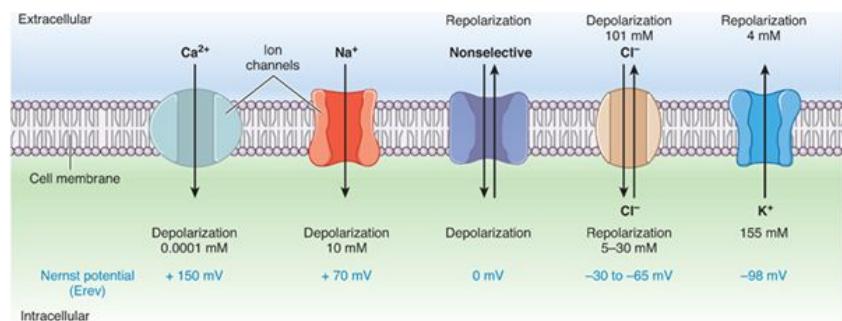


FIGURE 1.10 Ion channels that traverse the lipid bilayer to allow ion transport in response to a ligand or change in membrane potential. Sodium and calcium flow into the cell to facilitate depolarization while chloride and potassium have net outward flow to allow for repolarization. Non-selective channels carry multiple ions but favor repolarization at the cell's resting potential.

Because of their charge, most ions are relatively insoluble in cell membranes. Ions pass through cell membranes primarily through “ion channels” in transmembrane proteins. Ion channels are intermolecular spaces that extend through the entire cell membrane. Some channels are highly specific with respect to ions allowed to pass (sodium, potassium), whereas other channels allow all ions below a certain size to pass (**Table 1.4**). Neurotransmitter receptors such as those for γ -aminobutyric acid, glycine, glutamate, and others are activated upon the binding of the transmitter to open or close the channel to their specific anion or cation.

Movement of the ion alters the resting potential of the cell to facilitate or suppress the generation of an action potential.

TABLE 1.4

Diameters of ions, molecules, and channels

	Diameter (nm) ^a
Channel (average)	0.80
Water	0.30
Sodium (hydrated)	0.51
Potassium (hydrated)	0.40
Chloride (hydrated)	0.39
Glucose	0.86

^a1 nm = 10 Å.

Genes encoding the protein ion channels may be defective, leading to diseases such as cystic fibrosis (chloride channel defects), long Q-T interval syndrome (mutant potassium or [less commonly] sodium channels), hereditary nephrolithiasis (chloride channel), hereditary myopathies including myotonia congenital (chloride channel), and malignant hyperthermia (eg, the ryanodine receptor, the primary receptor releasing calcium from the sarcoplasmic reticulum)¹⁷ or the α_1 subunit of the dihydropyridine receptor encoded by the CACNA1S gene.¹⁸ The CACNA1S encoded calcium. Many drugs target ion channels, including common intravenous and inhalational anesthetics. Although details on the physiologic underpinning of most drugs is understood, the mechanism that underlies the action of inhalational anesthetics remains a well-studied mystery.^{19,20} Ion channels are discussed further in detail in [Chapter 3](#). Their interactions with general anesthetics are discussed in [Chapter 4](#).

Protein-Mediated Transport

Protein-mediated transport is responsible for movement of specific substrates across cell membranes. Indeed, carrier molecules are enzymes (specifically ATPases) that catalyze the hydrolysis of ATP. The most important of the ATPases is sodium-potassium ATPase, commonly called the sodium pump, which pumps sodium and potassium against their chemical gradients. Substances that are actively transported through cell membranes against a concentration gradient include ions (sodium, potassium, calcium, hydrogen, chloride, and magnesium), iodide (thyroid gland), carbohydrates, and amino acids.

P-glycoprotein is the primary transmembrane transporter, particularly for transporting drugs across the blood–brain barrier. Notably, the transport of morphine out of the CNS significantly slows the rate of rise and activity of morphine in the CNS.²¹ The ABC transporters (of which P-glycoprotein is a member) can be upregulated by long-term exposure to substrates including morphine and oxycodone contributing to tolerance.²² Virtually all transport of molecules against concentration gradients requires the assistance of proteins, which utilize energy provided by ATP to pump the molecule against the concentration gradient.

Sodium Ion Cotransport

Despite the widespread presence of sodium-potassium ATPase, the active transport of sodium ions in some tissues is coupled to the transport of other substances. For example, a carrier system present in the gastrointestinal tract and renal tubules will transport sodium ions only in combination with a glucose molecule. As such, glucose is returned to the circulation, thus preventing its excretion. Sodium ion cotransport of amino acids is an active transport mechanism that supplements facilitated diffusion of amino acids into cells. Epithelial cells lining the gastrointestinal tract and renal tubules are able to reabsorb amino acids into the circulation by this mechanism, thus preventing their excretion.

Other substances, including insulin, steroids, and growth hormone, influence amino acid transport by the sodium ion cotransport mechanism. For example, estradiol facilitates transport of amino acids into the musculature of the uterus, which promotes uterine and metamorphosis during pregnancy.

Aquaporins

Aquaporins are protein channels that permit water to freely flux across cell membranes.²³ In the absence of aquaporins, diffusion of water might not be sufficiently rapid for some physiologic processes. Genetic defects in aquaporins are responsible for several clinical diseases, including some cases of congenital cataracts²⁴ and nephrogenic diabetes insipidus.²⁵

Nucleus

The nucleus is mostly made up of the 46 chromosomes, except the nucleus of the egg cell, which contains 23. Each chromosome consists of a molecule of DNA covered with proteins including histones that tightly regulate DNA transcription. The nucleus is surrounded by a membrane that separates its contents from the cytoplasm. Nuclear pores allow transport of larger molecules, including RNA, and DNA, and proteins to pass between the nucleus and the cytoplasm.

The nucleolus is a non-membrane-bound structure within the nucleus responsible for the synthesis of ribosomes. Centrioles are present in the cytoplasm near the nucleus and coordinate the movement of chromosomes during cell division ([Figure 1.11](#)).

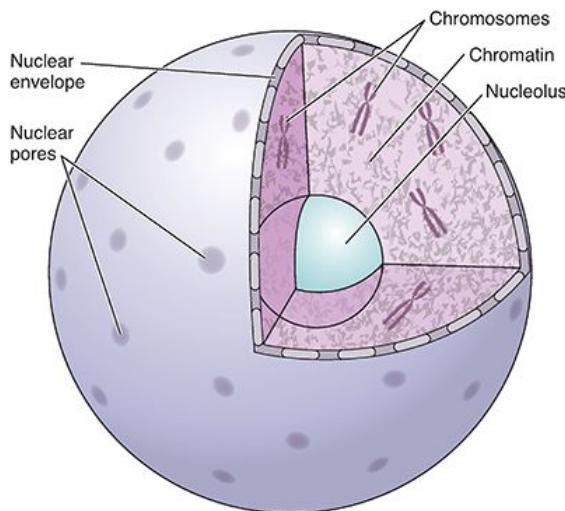


FIGURE 1.11 Contents of the cellular nucleus.

Structure and Function of DNA and RNA

The DNA consists of two complementary nucleotide chains composed of adenine, guanine, thymine, and cytosine ([Figure 1.12](#)).²⁶ The genetic message is determined by the sequence of nucleotides. The DNA is transcribed to RNA, which transfers the genetic message to the site of protein synthesis (ribosomes) in cytoplasm. All 3.2 billion base pairs of the human genome has been sequenced.²⁷ The protein encoding genes account for only 1% to 2% of our DNA. Our genome differs from that of chimpanzees by just 1%.²⁸ This explains so much!

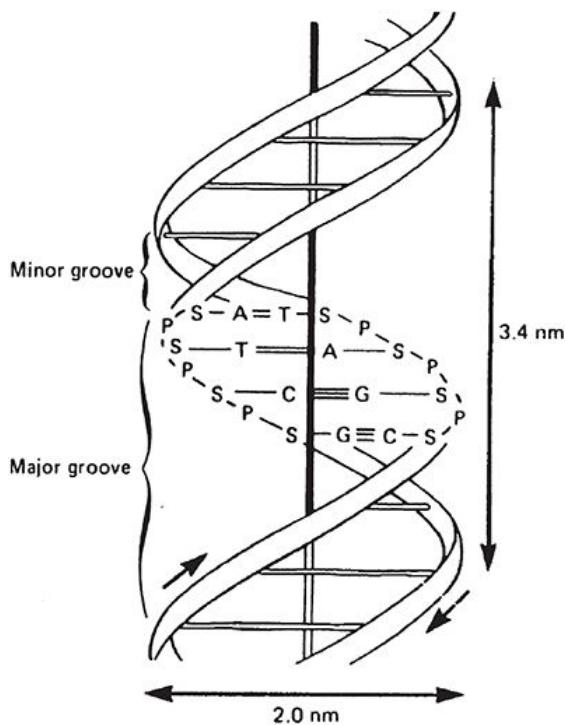


FIGURE 1.12 Double helical structure of DNA with adenine (A) bonding to thymine (T) and cytosine (C) to guanine (G). Republished with permission from Murray RK. Harper's Biochemistry. 23rd ed. Norwalk, CT: Appleton & Lange; 1990. Copyright © 1990 by Appleton & Lange.

The vast majority of our DNA consists of regulatory sequences, non-protein encoding RNA sequences (ribosomal RNA, transfer RNA and small nucleolar RNA), introns, and a considerable amount of DNA previously termed *junk* because it has no known function. Noncoding genes are transcribed to RNA but not translated to protein. There are short RNA sequences termed *microRNA* and long noncoding sequences called pseudogenes that can be transcribed from hundreds of base pairs. The physiologic functions are still being identified by include modulation of gene expression, protein function, and preservation of genomic stability in germ line cells.²⁹

Cytoplasm

The cytoplasm consists of water, electrolytes, and proteins including enzymes, lipids, and carbohydrates. About 70% to 80% of the cell volume is water. Cellular chemicals are dissolved in the water, and these substances can diffuse to all parts of the cell in this fluid medium. Proteins are, next to water, the most abundant substance in most cells, accounting for 10% to 20% of the cell mass. The cytoplasm contains numerous organelles with specific roles in cellular function.

Mitochondria

Mitochondria are the power-generating units of cells. They contain both the enzymes and substrates of the tricarboxylic acid cycle (Krebs cycle) and the electron transport chain. As a result, oxidative phosphorylation and synthesis of ATP are localized to mitochondria. The ATP leaves the mitochondria and diffuses throughout the cell, providing energy for cellular functions. Mitochondria consist of two lipid bilayers: the outer bilayer in contact with the cytoplasm and the inner layer that houses most of the biochemical machinery and the mitochondrial DNA. The space between these two membranes functions as a reservoir for protons created during electron transport. It is the movement of these protons back to the matrix, through the inner membrane, that drives the conversion of adenosine diphosphate to ATP, the primary form of intercellular energy, by ATP synthase.³⁰

Increased need for ATP in the cell leads to an increase in the number of mitochondria. A number of diseases are known to be based on aberrant mitochondrial function.³¹ The common element of mitochondrial diseases is aberrant cellular energetics. Mitochondria are exclusively inherited from the mother because sperm have no mitochondria. However, of the approximately 1,500 proteins responsible for mitochondrial function, only 13 are encoded by mitochondrial DNA. The balance is encoded in the nuclear DNA. Thus, the vast majority of mitochondrial diseases follow standard models of genetic inheritance.

Endoplasmic Reticulum

The endoplasmic reticulum is a complex lipid bilayer that wraps and folds creating tubules and vesicles in the cytoplasm. Ribosomes, composed mainly of RNA, attach to the outer portions of many parts of the endoplasmic reticulum membranes, serving as the sites for protein synthesis. The portion of the membrane containing these ribosomes is known as the *rough endoplasmic reticulum*. The part of the membrane that lacks ribosomes is the *smooth endoplasmic reticulum*. This smooth portion of the endoplasmic reticulum membrane functions in the synthesis of lipids, metabolism of carbohydrates, and other enzymatic processes. The sarcoplasmic reticulum is found in muscle cells, where it serves as a reservoir for calcium required for activation of the contractile apparatus.

Lysosomes

Lysosomes are lipid membrane enclosed organelles scattered throughout the cytoplasm. They function as an intracellular digestive system. Lysosomes are filled with digestive (hydrolytic) enzymes. When cells are damaged or die, these digestive enzymes cause autolysis of the remnants. Bactericidal substances in the lysosome kill phagocytized bacteria before they can cause cellular damage. These bactericidal substances include (1) lysozyme, which dissolves the cell membranes of bacteria; (2) lysoferrin, which binds iron and other metals that are essential for bacterial growth; (3) acid that has a pH of <4; and (4) hydrogen peroxide, which can disrupt some bacterial metabolic systems.

Lysosomal storage diseases are genetic disorders caused by inherited genetic defect in lysosomal function, resulting in accumulation of incompletely degraded macromolecules. There are more than 50 known lysosomal storage diseases, including Tay-Sachs, Gaucher, Fabry, and Niemann-Pick diseases.³²

Golgi Apparatus

The Golgi apparatus is a collection of membrane-enclosed sacs that are responsible for storing proteins and lipids as well as performing postsynthetic modifications including glycosylation and phosphorylation. Proteins synthesized in the rough endoplasmic reticulum are transported to the Golgi apparatus, where they are stored in highly concentrated packets (secretory vesicles) for subsequent release into the cell's cytoplasm, or transport to the surface for extracellular release via exocytosis. Exocytic vesicles continuously release their content, whereas secretory vesicles store the packaged material until a triggering signal is received. Neurotransmitter release is a highly relevant (to anesthesia) example of regulated secretion. The Golgi apparatus is also responsible for creating lysosomes.

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Basic Principles of Pharmacology

Pamela Flood • Steven L. Shafer

This chapter combines Dr. Stoelting's original elegant description of pharmacology with mathematical underpinnings first presented by Dr. Shafer¹ in 1997 and most recently in *Miller's Anesthesia*.^{2,3} The combination of approaches sets a foundation for the pharmacology presented in the subsequent chapters. It also explains the fundamental principles of drug behavior and drug interaction that govern our daily practice of anesthesia.

Receptor Theory

A drug that *activates* a receptor by binding to that receptor is called an **agonist**. Most agonists bind through a combination of ionic, hydrogen, and van der Waals interactions (the sum of the attractive or repulsive forces between molecules), making them reversible. Rarely, an agonist will bind covalently to the receptor, rendering the interaction irreversible. Receptors are often envisioned as proteins that are either unbound or are bound to the agonist ligand. When the receptor is bound to the agonist ligand, the effect of the drug is produced. When the receptor is not bound, there is no effect. The receptor state is seen as binary: It is either unbound, resulting in one conformation, or it is bound, resulting in another conformation. Agonists are often portrayed as simply activating a receptor (**Figure 2.1**). In this view, the magnitude of the drug effect reflects the total number of receptors that are bound. In this simplistic view, the “most” drug effect occurs when every receptor is bound.

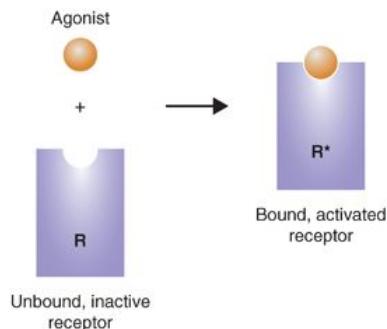


FIGURE 2.1 The interaction of a receptor with an agonist may be portrayed as a binary bound versus unbound receptor. The unbound receptor is portrayed as inactive. When the receptor is bound to the agonist ligand, it becomes the activated, R^* , and mediates the drug effect. This view is too simplistic, but it permits understanding of basic agonist behavior.

This simple view helps to understand the action of an antagonist (**Figure 2.2**). An **antagonist** is a drug that binds to the receptor without activating the receptor. Antagonists typically bind with ionic, hydrogen, and van der Waals interactions, rendering them reversible. Antagonists block the action of agonists simply by getting in the way of the agonist, preventing the agonist from binding to the receptor and producing the drug effect. **Competitive antagonism** is present when increasing concentrations of the antagonist progressively inhibit the response to the agonist. This causes a rightward displacement of the agonist dose-response (or concentration-response) relationship. **Noncompetitive antagonism** is present when, after administration of an antagonist, even high concentrations of agonist cannot completely overcome the antagonism. In this instance, either the agonist is bound irreversibly (and probably covalently) to the receptor site or it binds to a different site on the molecule and the interaction is allosteric (occurring at another site that fundamentally alters the activity of the receptor). Noncompetitive antagonism causes both a rightward shift of the dose-

response relationship as well as a decreased maximum efficacy of the concentration versus response relationship.

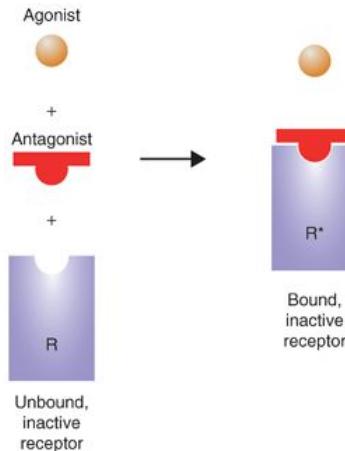


FIGURE 2.2 The simple view of receptor activation also explains the action of antagonist. In this case, the antagonist (red) binds to the receptor, but the binding does not cause activation. However, the binding of the antagonist blocks the agonist from binding, and thus blocks agonist drug effect. If the binding is reversible, this is competitive antagonism. If it is not reversible, then it is noncompetitive antagonism.

Although this simple view of activated and inactivated receptors explains agonists and antagonists, it has a more difficult time with **partial agonists** and **inverse agonists** (Figure 2.3). A partial agonist is a drug that binds to a receptor (usually at the agonist site) where it activates the receptor but not as much as a full agonist. Even at supramaximal doses, a partial agonist cannot cause the full drug effect. Partial agonists may also have antagonist activity in which case they are also called **agonist-antagonists**. When a partial agonist is administered with a full agonist, it decreases the effect of the full agonist. For example, butorphanol acts as a partial agonist at the μ -opioid receptor. Given alone, butorphanol is a modestly efficacious analgesic. Given along with fentanyl, it will partly reverse the fentanyl analgesia. Individuals using high doses of full agonist opioids withdraw after receiving buprenorphine. Inverse agonists bind at the same site as the agonist (and likely compete with it), but they produce the opposite effect of the agonist. Inverse agonists “turn off” the constitutive activity of the receptor. The simple view of receptors as bound or unbound does not explain partial agonists or inverse agonists.

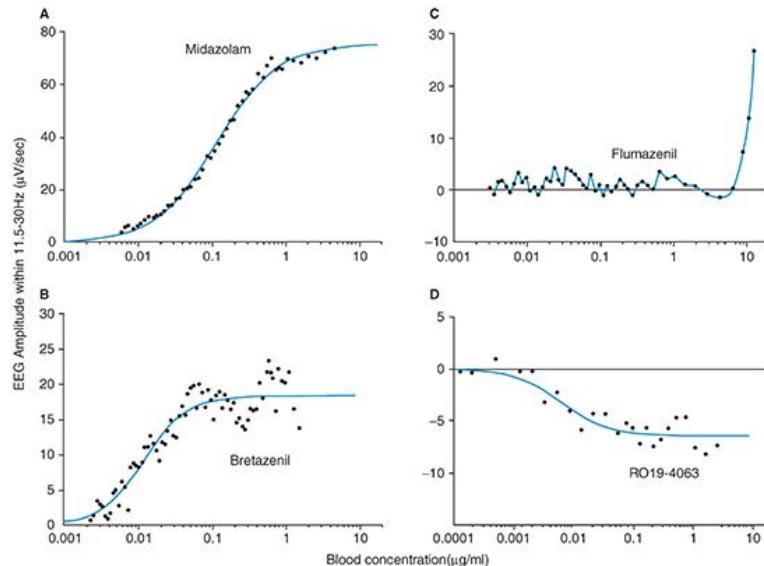


FIGURE 2.3 The concentration versus electroencephalogram (EEG) response relationship for four benzodiazepine ligands: midazolam (full agonist), bretazenil (partial agonist), flumazenil (competitive antagonist), and RO 19-4063 (inverse agonist). *Reprinted from Shafer SL. Principles of pharmacokinetics and pharmacodynamics. In: Longnecker DE, Tinker JH, Morgan GE, eds. Principles and Practice of Anesthesiology. 2nd ed. St Louis, MO: Mosby-Year Book; 1997:1159, based on Mandema JW, Kuck MT, Danhof M. In vivo modeling of the pharmacodynamic interaction between benzodiazepines which differ in intrinsic efficacy. J Pharmacol Exp Ther. 1992;261(1):56-61. Copyright © 1997 Elsevier. With permission.*

It turns out that receptors have many natural conformations, and they naturally fluctuate between these different conformations (**Figure 2.4**). Some of the conformations are associated with the pharmacologic effect, and some are not. In the example shown, the receptor only has two states: an inactive state and an active state that produces the same effect as if an agonist were bound to the receptor, although at a reduced level because the receptor only spends 20% of its time in this activated state.

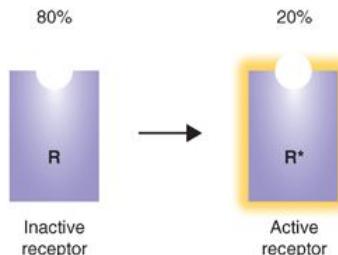


FIGURE 2.4 Receptors have multiple states, and they switch spontaneously between them. In this case, the receptor has just two states. It spends 80% of the time in the inactive state and 20% of the time in the active state in the absence of any ligand.

In this view, ligands do not cause the receptor shape to change. That happens spontaneously. However, ligands change the ratio of active to inactive states by (thermodynamically) favoring one of the states. **Figure 2.5** shows the receptor as seen in **Figure 2.4** in the presence of an agonist, a partial agonist, an antagonist, and an inverse agonist. Presence of the full agonist causes the conformation of the active state to be strongly favored, causing the receptors to be in this state nearly 100% of the time. The partial agonist is not as effective in stabilizing the receptor in the active state, so the bound receptor only spends 50% of its time in this state. The antagonist does not favor either state; it just gets in the way of binding (as before; see **Figure 2.2**). The inverse agonist favors the inactive state, reversing the baseline receptor activity.

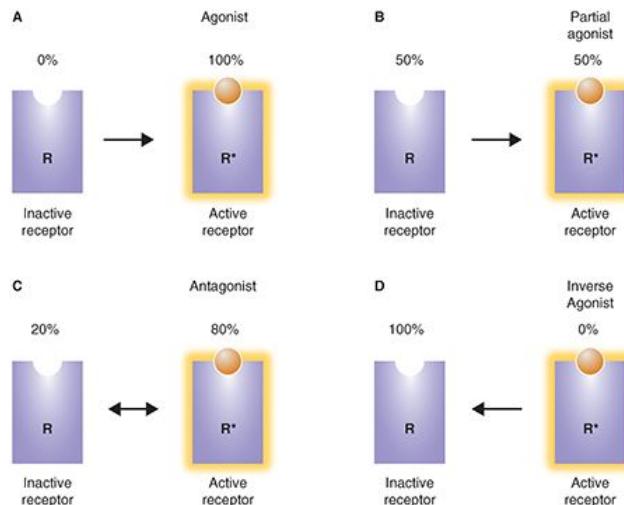


FIGURE 2.5 The action of agonists (A), partial agonists (B), antagonists (C), and inverse agonists (D) can be interpreted as changing the balance between the active and inactive forms of the receptor. In this case, in

the absence of agonist, the receptor is in the activated state 20% of the time. This percentage changes based on nature of the ligand bound to the receptor.

Using this information, we can now interpret the action of several ligands for the benzodiazepine receptor (see [Figure 2.3](#)). The actions include full agonism (midazolam), partial agonism (bretazenil), competitive antagonism (flumazenil), and inverse agonism (RO 19-4063). This range of actions can be explained by considering receptor states. Assume that the γ -aminobutyric acid (GABA) receptor has several conformations, one of which is particularly sensitive to endogenous GABA. Typically, there are some GABA receptors in this more sensitive conformation. As a full agonist, midazolam causes nearly all of the GABA receptors to be in the confirmation with increased sensitivity to GABA. Bretazenil does the same thing but not as well. Even when every benzodiazepine receptor is occupied by bretazenil, fewer GABA receptors are in the more sensitive confirmation. Bretazenil simply does not favor that conformation as well as midazolam. When flumazenil is in the binding pocket, it does not change the relative probabilities of the receptor being in any conformation. Flumazenil just gets in the way of other drugs that would otherwise bind to the pocket. RO 19-4063 actually decreases the number of GABA receptors in the more sensitive conformation. Usually, some of them are in this more sensitive conformation, but that number is decreased by the inverse agonist RO 19-4063 (which was never developed as a drug because endogenous benzodiazepines, although anticipated, have not been described). The notion of receptors having multiple conformations with distinct activity, and drugs acting through favoring particular conformations, helps to understand the action of agonists, partial agonists, antagonists, and inverse agonists.

Receptor Action

The number for receptors in cell membranes is dynamic and increases (upregulates) or decreases (downregulates) in response to specific stimuli. For example, a patient with pheochromocytoma has an excess of circulating catecholamines. In response, there is a decrease in the numbers of β -adrenergic receptors in cell membranes in an attempt to maintain homeostasis. Likewise, prolonged treatment of asthma with a β -agonist may result in tachyphylaxis (decreased response to the same dose of β -agonist, often indistinguishable from **tolerance**) because of the decrease in β -adrenergic receptors. Conversely, lower motor neuron injury causes an increase in the number of nicotinic acetylcholine receptors in the neuromuscular junction, leading to an exaggerated response to succinylcholine. Changing receptor numbers is one of many mechanisms that contribute to variability in response to drugs.

Receptor Types

Receptors for drug action can be classified by location. Many of the receptors thought to be the most critical for anesthetic action are located in the lipid bilayer of cell membranes. For example, opioids, intravenous sedative hypnotics, benzodiazepines, β -blockers, catecholamines, and muscle relaxants (most of which are antagonists) all interact with membrane-bound receptors. Some receptors are intracellular proteins. Drugs such as caffeine, insulin, steroids, theophylline, and milrinone interact with intracellular proteins. Circulating proteins can also be drug targets. The coagulation cascade comprises an ensemble of circulating proteins, many of which are therapeutic targets for modifying coagulation.

There are also drugs that do not interact with proteins at all. Stomach antacids such as sodium citrate simply work by changing gastric pH. Chelating drugs work by binding divalent cations. Iodine kills bacteria by osmotic pressure (intracellular desiccation, which is why it is best to let iodine prep solutions dry), and intravenous sodium bicarbonate changes plasma pH. The mechanism of action of these drugs does not involve receptors per se, and hence, these drugs will not be further considered in this section.

Proteins are small machines whose cogs, cams, and wheels catalyze enzymatic reactions, permit ions to traverse cell membranes, exert mechanical force, or the myriad of other protein-based activities. When a drug binds to a receptor, it changes the activity of the machine, typically by enhancing its activity (eg, propofol increases the sensitivity of the GABA_A receptor to GABA, the endogenous ligand), decreasing its activity (ketamine decreases the activity of the N-methyl-D-aspartate [NMDA] receptor), or triggering a chain

reaction (opioid binding to the μ -opioid receptor activates an inhibitory G protein that decreases adenylyl cyclase activity). The protein's response to binding of the drug is responsible for the drug effect.

Pharmacokinetics

Pharmacokinetics is the quantitative study of the absorption, distribution, metabolism, and excretion of injected and inhaled drugs and their metabolites. *Pharmacokinetics describes what the body does to the drug.* Pharmacodynamics is the quantitative study of the body's response to a drug. *Pharmacodynamics describes what the drug does to the body.* This section introduces the basic principles of pharmacokinetics. The next section discusses the basic principles of pharmacodynamics.

Pharmacokinetics determines the concentration of a drug in the plasma or at the site of drug effect. Pharmacokinetic variability is a significant component of patient-to-patient variability in drug response. Pharmacokinetic variability may result from genetic modifications in metabolism; interactions with other drugs; or diseases of the liver, kidneys, or other organs of metabolism.⁴

The basic principles of pharmacokinetics are absorption, metabolism, distribution, and elimination. These processes are fundamental to all drugs. They can be described in basic physiologic terms or using mathematical models. Each serves a purpose. Physiology can be used to predict how changes in organ function will affect the disposition of drugs. Mathematical models can be used to calculate the concentration of drug in the blood or tissue following any arbitrary dose at any arbitrary time. We initially tackle the physiologic principles that govern distribution, metabolism, elimination, and absorption, in that order. We then turn to the mathematical models.

Distribution

Intravenously administered drugs mix with body tissues and are immediately diluted from the concentrated injectate in the syringe to the more dilute concentration measured in the plasma or tissue. This initial distribution (within 1 minute) after bolus injection is considered mixing within the “central compartment” (**Figure 2.6**). The central compartment is physically composed of those elements of the body that dilute the drug within the first minute after injection: the venous blood volume of the arm, the volume of the great vessels, the heart, the lung, and the upper aorta, and whatever uptake of drug occurs in the first passage through the lungs. Many of these volumes are fixed regardless of the drug that is given. The lungs are different. Drugs that are highly fat soluble may be avidly taken up in the first passage through the lung, reducing the concentration measured in the arterial blood. This results in an apparent increase in size of the central compartment. For example, first-pass pulmonary uptake of the initial dose of lidocaine, propranolol, meperidine, fentanyl, sufentanil, and alfentanil exceeds 65% of the dose.⁵

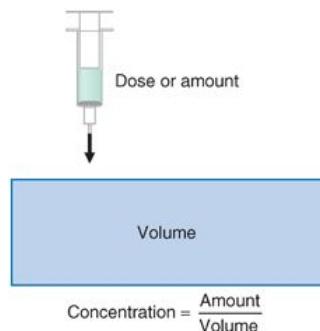


FIGURE 2.6 The central volume is the volume that intravenously injected drug initially mixes into. Reprinted from Shafer SL, Flood P, Schwinn DA. Basic principles of pharmacology. In: Miller RD, Eriksson LI, Fleisher LA, et al, eds. Miller's Anesthesia. Vol 1. 7th ed. Philadelphia, PA: Churchill Livingstone; 2010:479-514, with permission. Copyright © 2010 Elsevier. With permission.

The body is a complex space, and mixing within the myriad body fluids and tissues is an ongoing process. The central compartment is the small initial mixing volume. Several minutes later, the drug will fully

mix with the entire blood volume. However, it may take hours or even days for the drug to fully mix with all bodily tissues because some tissues have very low perfusion.

In the process of mixing, molecules are drawn to other molecules, some with specific binding sites. A drug that is polar will be drawn to water, where the polar water molecules find a low-energy state by associating with the charged aspects of the molecule. A drug that is nonpolar has a higher affinity for fat, where van der Waals binding provides numerous weak binding sites. Many anesthetic drugs are highly fat soluble and poorly soluble in water. High fat solubility means that the molecule will have a large volume of distribution because it will be preferentially taken up by fat, diluting the concentration in the plasma. The extreme example of this is propofol, which is almost inseparable from fat. The capacity of body fat to hold propofol is so vast that in some studies, the total volume of distribution of propofol has been reported as exceeding 5,000 L. Of course, nobody has a total volume of 5,000 L! It is important to understand that those 5,000 L refer to imaginary liters of plasma required to dilute the initial dose of propofol to achieve the measured concentration. Because propofol is so fat soluble, a large amount of propofol is held in the body's fatty tissues, with just a tiny fraction measured in the plasma.

Following bolus injection, the drug initially goes to the tissues that receive the bulk of arterial blood flow: the brain, heart, kidneys, and liver. These tissues are often called the **vessel-rich group**. The rapid blood flow to these highly perfused tissues ensures that the tissue drug concentration rapidly equilibrates with arterial blood. However, for highly lipid-soluble drugs, the capacity of the fat to hold the drug greatly exceeds the capacity of highly perfused tissues. Initially, the fat compartment is almost invisible because the blood supply to fat is quite limited. However, with time, the fat gradually absorbs more and more drug, sequestering it away from the highly perfused tissues. This redistribution of drug from the highly perfused tissue to the fat accounts for a substantial part of the offset of drug effect following a bolus of an intravenous anesthetic or fat-soluble opioid (eg, fentanyl). Muscles play an intermediate role in this process, having (at rest) blood flow that is intermediate between highly perfused tissues and fat, and also having intermediate solubility for lipophilic drugs.

Protein Binding

Most drugs are bound to some extent to plasma proteins, primarily albumin, α_1 -acid glycoprotein, and lipoproteins.⁶ Most acidic drugs bind to albumin, whereas basic drugs bind to α_1 -acid glycoprotein. Protein binding effects both the distribution of drugs (because only the free or unbound fraction can readily cross cell membranes) and the apparent potency of drugs, again because it is the free fraction that determines the concentration of bound drug on the receptor.

The extent of protein binding parallels the lipid solubility of the drug. This is because drugs that are hydrophobic are more likely to bind to proteins in the plasma and to lipids in the fat. For intravenous anesthetic drugs, which tend to be quite potent, the number of available protein binding sites in the plasma vastly exceeds the number of sites actually bound. As a result, the fraction bound is not dependent on the concentration of the anesthetic and only dependent on the protein concentration.

Binding of drugs to plasma albumin is nonselective, and drugs with similar physicochemical characteristics may compete with each other and with endogenous substances for the same protein binding sites. For example, sulfonamides can displace unconjugated bilirubin from binding sites on albumin, leading to the risk of bilirubin encephalopathy in the neonate.

Age, hepatic disease, renal failure, and pregnancy can decrease plasma protein concentration. Alterations in protein binding are important only for drugs that are highly protein bound (eg, >90%). For such drugs, the free fraction changes as an inverse proportion with a change in protein concentration. If the free fraction is 2% in the normal state, then in a patient with 50% decrease in plasma proteins, the free fraction will increase to 4%, a 100% increase.

Theoretically, an increase in free fraction of a drug may increase the pharmacologic effect of the drug, but in practice, it is far from certain that there will be any change in pharmacologic effect at all. The reason is that it is the unbound fraction that equilibrates throughout the body, including with the receptor. Plasma proteins only account for a small portion of the total binding sites for drug in the body. Because the free drug **concentration** in the plasma and tissues represents partitioning with all binding sites, not just the plasma

binding sites, the actual free drug concentration that drives drug on and off receptors may change fairly little with changes in plasma protein concentration.

Metabolism

Metabolism converts pharmacologically active, lipid-soluble drugs into water-soluble and usually pharmacologically inactive metabolites. However, this is not always the case. For example, diazepam and propranolol may be metabolized to active compounds. Morphine-6-glucuronide, a metabolite of morphine, is a more potent opioid than morphine itself. In some instances, an inactive parent compound (prodrug) is metabolized to an active drug. This is the case with codeine, which is an exceedingly weak opioid. Codeine is metabolized to morphine, which is responsible for the analgesic effects of codeine.

Pathways of Metabolism

The four basic pathways of metabolism are (1) oxidation, (2) reduction, (3) hydrolysis, and (4) conjugation. Traditionally, metabolism has been divided into phase I and phase II reactions. Phase I reactions include oxidation, reduction, and hydrolysis, which increase the drug's polarity prior to the phase II reactions. Phase II reactions are conjugation reactions that covalently link the drug or metabolites with a highly polar molecule (carbohydrate or an amino acid) that renders the conjugate more water-soluble for subsequent excretion.

Hepatic microsomal enzymes are responsible for the metabolism of most drugs. Other sites of drug metabolism include the plasma (Hofmann elimination, ester hydrolysis), lungs, kidneys, and gastrointestinal tract and placenta (tissue esterases). Hepatic microsomal enzymes, which participate in the metabolism of many drugs, are located principally in hepatic smooth endoplasmic reticulum. These microsomal enzymes are also present in the kidneys, gastrointestinal tract, and adrenal cortex. Microsomes are vesicle-like artifacts reformed from pieces of the endoplasmic reticulum bilayer sliced apart as cells are cut up in a blender. Microsomal enzymes are those enzymes that are concentrated in these vesicle-like artifacts.

Phase I Enzymes

Enzymes responsible for phase I reactions include cytochrome P450 (CYP) enzymes, non-CYP enzymes, and flavin-containing monooxygenase enzymes. The CYP enzyme system is a large family of membrane-bound proteins containing a heme cofactor that catalyzes the metabolism of compounds. The P450 enzymes are predominantly hepatic microsomal enzymes, although there are also mitochondrial P450 enzymes. The designation CYP is derived from their characteristic absorption peak at 450 nm when heme is combined with carbon monoxide. The CYP system is also known as the mixed function oxidase system because it involves both oxidation and reduction steps; the most common reaction catalyzed by CYP is the monooxygenase reaction, for example, insertion of one atom of oxygen into an organic substrate while the other oxygen atom is reduced to water. The CYP functions as the terminal oxidase in the electron transport chain.

Individual CYP enzymes have evolved from a common protein.⁷ The CYP enzymes, often called **CYPs**, that share more than 40% sequence homology are grouped in a family designated by a number (eg, “CYP2”), those that share more than 55% homology are grouped in a subfamily designated by a letter (eg, “CYP2A”), and individual CYP enzymes are identified by a third number (eg, “CYP2A6”). Ten isoforms of CYP are responsible for the oxidative metabolism of most drugs. The preponderance of CYP activity for anesthetic drugs is generated by CYP3A4, which is the most abundantly expressed P450 isoform, comprising 20% to 60% of total P450 activity. The P450 3A4 metabolizes more than one-half of all currently available drugs, including opioids (alfentanil, sufentanil, fentanyl), benzodiazepines, local anesthetics (lidocaine, ropivacaine), immunosuppressants (cyclosporine), and antihistamines (terfenadine).

Drugs can alter the activity of these enzymes through induction and inhibition. Induction occurs through increased expression of the enzymes. For example, phenobarbital induces microsomal enzymes and thus can render drugs less effective through increased metabolism. Conversely, other drugs directly inhibit enzymes, increasing the exposure to their substrates. Famously, grapefruit juice (not exactly a drug) inhibits CYP 3A4, possibly increasing the concentration of anesthetics and other drugs.

Oxidation

CYP enzymes are crucial for oxidation reactions. These enzymes require an electron donor in the form of reduced nicotinamide adenine dinucleotide and molecular oxygen for their activity. The molecule of oxygen is split, with one atom of oxygen oxidizing each molecule of drug and the other oxygen atom being incorporated into a molecule of water. Examples of oxidative metabolism of drugs catalyzed by CYP enzymes include hydroxylation, deamination, desulfuration, dealkylation, and dehalogenation. Demethylation of morphine to normorphine is an example of oxidative dealkylation. Dehalogenation involves oxidation of a carbon-hydrogen bond to form an intermediate metabolite that is unstable and spontaneously loses a halogen atom. Halogenated volatile anesthetics are susceptible to dehalogenation, leading to release of bromide, chloride, and fluoride ions. Aliphatic oxidation is oxidation of a side chain. For example, oxidation of the side chain of thiopental converts the highly lipid-soluble parent drug to the more water-soluble carboxylic acid derivative. Thiopental also undergoes desulfuration to pentobarbital by an oxidative step.

Epoxide intermediates in the oxidative metabolism of drugs are capable of covalent binding with macromolecules and may be responsible for some drug-induced organ toxicity, such as hepatic dysfunction. Normally, these highly reactive intermediates have such a transient existence that they exert no biologic action. When enzyme induction occurs, however, large amounts of reactive intermediates may be produced, leading to organ damage. This is especially likely to occur if the antioxidant glutathione, which is in limited supply in the liver, is depleted by the reactive intermediates.

Reduction

The CYP enzymes are also essential for reduction reactions. Under conditions of low oxygen partial pressures, CYP enzymes transfer electrons directly to a substrate such as halothane rather than to oxygen. This electron gain imparted to the substrate occurs only when insufficient amounts of oxygen are present to compete for electrons.

Conjugation

Conjugation with glucuronic acid involves CYP enzymes. Glucuronic acid is synthesized from glucose and added to lipid-soluble drugs to render them water-soluble. The resulting water-soluble glucuronide conjugates are then excreted in bile and urine. In premature infants, reduced microsomal enzyme activity interferes with conjugation, leading to neonatal hyperbilirubinemia and the risk of bilirubin encephalopathy. The reduced conjugation ability of the neonate increases the effect and potential toxicity of drugs that are normally inactivated by conjugation with glucuronic acid.

Hydrolysis

Enzymes responsible for hydrolysis of drugs, usually at an ester bond, do not involve the CYP enzymes system. Hydrolysis often occurs outside of the liver. For example, remifentanil, succinylcholine, esmolol, and the ester local anesthetics are cleared in the plasma and tissues via ester hydrolysis.

Phase II Enzymes

Phase II enzymes include glucuronosyltransferases, glutathione-S-transferases, *N*-acetyl-transferases, and sulfotransferases. Uridine diphosphate glucuronosyltransferase catalyzes the covalent addition of glucuronic acid to a variety of endogenous and exogenous compounds, rendering them more water-soluble. Glucuronidation is an important metabolic pathway for several drugs used during anesthesia, including propofol, morphine (yielding morphine-3-glucuronide and the pharmacologically active morphine-6-glucuronide), and midazolam (yielding the pharmacologically active α_1 -hydroxymidazolam). Glutathione-S-transferase enzymes are primarily a defensive system for detoxification and protection against oxidative stress. *N*-Acetylation catalyzed by *N*-acetyl-transferase is a common phase II reaction for metabolism of heterocyclic aromatic amines (particularly serotonin) and arylamines, including the inactivation of isoniazid.

Hepatic Clearance

The rate of metabolism for most anesthetic drugs is proportional to drug concentration, rendering the clearance of the drug constant (ie, independent of dose). This is a fundamental assumption for anesthetic pharmacokinetics. Exploring this assumption will provide insight into the critical role of clearance in governing the metabolism of drugs.

Although the metabolic capacity of the body is large, it is not possible that metabolism is *always* proportional to drug concentration because the liver does not have infinite metabolic capacity. At some rate of drug flow into the liver, the organ will be metabolizing drug as fast as the metabolic enzymes in the organ allow. At this point, metabolism can no longer be proportional to concentration because the metabolic capacity of the organ has been exceeded.

Understanding metabolism starts with a simple mass balance: The rate at which drug flows *out* of the liver must be the same as the rate at which drug flows *into* the liver minus the rate at which the liver metabolizes drug. The rate at which drug flows into the liver is liver blood flow, Q , times the concentration of drug flowing in, C_{inflow} . The rate at which drug flows out of the liver is liver blood flow, Q , times the concentration of drug flowing out, $C_{outflow}$. The rate of hepatic metabolism by the liver, R , is the difference between the drug concentration flowing into the liver and the drug concentration flowing out of the liver, times the rate of liver blood flow:

$$\text{Rate of drug metabolism} = R = Q(C_{inflow} - C_{outflow})$$

Equation 2.1

This relationship is illustrated in [Figure 2.7](#).

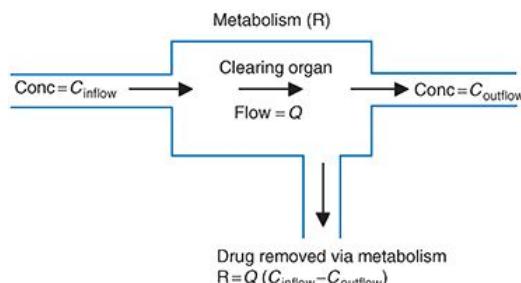


FIGURE 2.7 The relationship between drug rate of metabolism can be computed as the rate of liver blood flow times the difference between the inflowing and outflowing drug concentrations. This is a common approach to analyzing metabolism or tissue uptake across an organ in mass-balance pharmacokinetic studies. *Reprinted from Shafer SL, Flood P, Schwinn DA. Basic principles of pharmacology. In: Miller RD, Eriksson LI, Fleisher LA, Wiener-Kronish JP, Young WL, eds. Miller's Anesthesia. Vol 1. 7th ed. Philadelphia, PA: Churchill Livingstone; 2010:479-514. Copyright © 2010 Elsevier. With permission.*

Metabolism can be saturated because the liver does not have infinite metabolic capacity. A common equation used for this saturation processes is as follows:

$$\text{Response} = \frac{C}{C_{50} + C}$$

Equation 2.2

“Response” in [Equation 2.2](#) varies from 0 to 1, depending on the value of C . In this context, Response is the fraction of maximal metabolic rate. Response = 0 means no metabolism, and response = 1 means metabolism at the maximal possible rate. C refers to whatever is driving the response. In this chapter, C means drug concentration. When C is 0, the response is 0. If C is greater than 0 but much less than C_{50} , the denominator

is approximately C_{50} and the response is nearly proportional to C : $\text{Response} \approx \frac{C}{C_{50}}$. If we increase C even further to exactly C_{50} , then the response is $\frac{C_{50}}{C_{50} + C_{50}} = 0.5$, which is simply 0.5. That is where the name “ C_{50} ” comes from:

It is the concentration associated with 50% response. As C becomes much greater than C_{50} , the equation

approaches $\frac{C}{C}$, which is 1. The shape of this relationship is shown in [Figure 2.8](#). The relationship is nearly linear at low concentrations, but at high concentrations, the response saturates at 1.

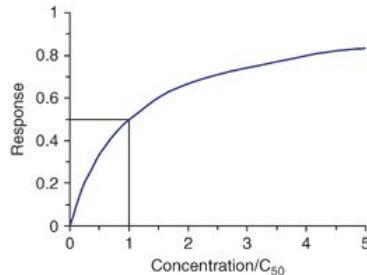


FIGURE 2.8 The shape of the saturation equation. Reprinted from Shafer SL, Flood P, Schwinn DA. Basic principles of pharmacology. In: Miller RD, Eriksson LI, Fleisher LA, Wiener-Kronish JP, Young WL, eds. Miller's Anesthesia. Vol 1. 7th ed. Philadelphia, PA: Churchill Livingstone; 2010:479-514. Copyright © 2010 Elsevier. With permission.

To understand hepatic clearance, we must understand the relationship between hepatic metabolism and drug concentration. But what concentration determines the rate of metabolism: the concentration flowing into the liver, the average concentration within the liver, or the concentration flowing out of the liver? All have been used, but the most common views the rate of metabolism as a function of the concentration flowing *out* of the liver, C_{outflow} . The rationale for using C_{outflow} is the same as the rationale for using end tidal anesthetic concentration to assess the steady state concentration in the lungs.

We can expand our equation of metabolism to include the observation that the rate of metabolism, R , approaches saturation at the maximum metabolic rate, V_m , as a function of C_{outflow} :

$$\begin{aligned} \text{Rate of drug metabolism} = R &= Q(C_{\text{inflow}} - C_{\text{outflow}}) = \\ &V_m \frac{C_{\text{outflow}}}{K_m + C_{\text{outflow}}} \end{aligned} \quad \text{Equation 2.3}$$

The saturation equation appears at the end of the [Equation 2.3](#) equation. The V_m is the maximum possible

metabolic rate. The saturation part of this equation, $\frac{C_{\text{outflow}}}{K_m + C_{\text{outflow}}}$, determines fraction of the maximum metabolic rate. K_m , the "Michaelis constant," is the outflow concentration at which the metabolic rate is 50% of the maximum rate (V_m). This relationship is shown in [Figure 2.9](#). The x -axis is the outflow concentration, C_{outflow} , as a fraction K_m . The y -axis is the rate of drug metabolism as a fraction of V_m . By normalizing the x - and y -axis in this manner, the relationship shown in [Figure 2.9](#) is true for all values of V_m and K_m . As long as the outflow concentration is less than one-half of K_m (true for almost all anesthetic drugs), there is a nearly proportional change in metabolic rate with a proportional change in outflow concentration. Another interpretation is that metabolism will be proportional to concentration as long as the metabolic rate is less than one-third of the maximum metabolic capacity.

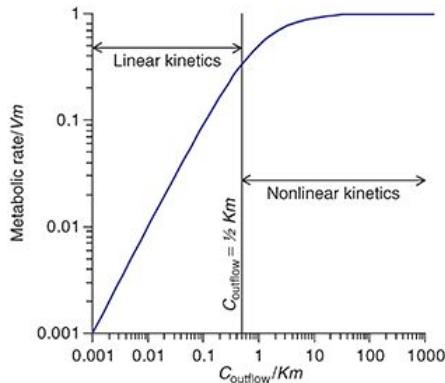


FIGURE 2.9 The relationship between concentration, here shown as a fraction of the Michaelis constant (K_m), and drug metabolism, here shown as a fraction of the maximum rate (V_m). Metabolism increases proportionally with concentration as long as the outflow concentration is less than half K_m , which corresponds to a metabolic rate that is roughly one-third of the maximal rate. Metabolism is proportional to concentration, meaning that clearance is constant, for typical doses of all intravenous drugs used in anesthesia. *Reprinted from Shafer SL, Flood P, Schwinn DA. Basic principles of pharmacology. In: Miller RD, Eriksson LI, Fleisher LA, Wiener-Kronish JP, Young WL, eds. Miller's Anesthesia. Vol 1. 7th ed. Philadelphia, PA: Churchill Livingstone; 2010:479-514. Copyright © 2010 Elsevier. With permission.*

So far, we have talked about the rate of metabolism and not about hepatic clearance. If the liver could completely extract the drug from the afferent flow, then clearance would equal liver blood flow, Q . However, the liver cannot remove every last drug molecule. There is always some drug in the effluent plasma. The

fraction of inflowing drug extracted by the liver is $\frac{C_{inflow} - C_{outflow}}{C_{inflow}}$. This is called the **extraction ratio**. Clearance is the amount of blood completely cleared of drug per unit time. We can calculate clearance as the liver blood flow times the extraction ratio:

$$\text{Clearance} = Q \times ER = Q \left(\frac{C_{inflow} - C_{outflow}}{C_{inflow}} \right)$$

Equation 2.4

With this basic understanding of clearance, let us divide each part of [Equation 2.3](#) by C_{inflow} :

$$\begin{aligned} \frac{\text{Rate of drug metabolism}}{C_{inflow}} &= \frac{R}{C_{inflow}} = \\ Q \left(\frac{C_{inflow} - C_{outflow}}{C_{inflow}} \right) &= \frac{C_{outflow}}{C_{inflow}} \left(\frac{V_m}{K_m + C_{outflow}} \right) \end{aligned}$$

Equation 2.5

The third term in the above equation is clearance as defined in [Equation 2.4](#): Q times the extraction ratio. Thus, each term in [Equation 2.4](#) must be clearance. Let us consider them in order.

$$\text{Clearance} = \frac{\text{Rate of drug metabolism}}{C_{inflow}}$$

The first term tells us that $\frac{\text{Rate of drug metabolism}}{C_{inflow}}$. This indicates that clearance is a proportionality constant that relates inflowing (eg, arterial) concentration to the rate of metabolism. If we want to maintain a given steady-state arterial drug concentration, we must infuse drug at the same rate that it is being metabolized. With this understanding, we can rearrange the equation to say the following: Infusion rate = metabolic rate = Clearance $\times C_{inflow}$. Thus, the infusion rate to maintain a given arterial concentration (C_{inflow}) is the clearance times the desired concentration.

The third and fourth terms

$$\text{Clearance} = Q \left(\frac{C_{\text{inflow}} - C_{\text{outflow}}}{C_{\text{inflow}}} \right)$$

and

$$\text{Clearance} = \frac{C_{\text{outflow}}}{C_{\text{inflow}}} \left(\frac{V_m}{K_m + C_{\text{outflow}}} \right)$$

$$\frac{C_{\text{inflow}} - C_{\text{outflow}}}{C_{\text{inflow}}}$$

are particularly interesting when taken together. Remembering that $\frac{C_{\text{inflow}} - C_{\text{outflow}}}{C_{\text{inflow}}}$ is the extraction ratio, these equations relate clearance to liver blood flow and the extraction ratio, as shown in [Figure 2.10](#).⁸ For drugs with an extraction ratio of nearly 1 (eg, propofol), a change in liver blood flow produces a nearly proportional change in clearance. For drugs with a low extraction ratio (eg, alfentanil), clearance is nearly independent of the rate of liver blood flow. This makes intuitive sense. If nearly 100% of the drug is extracted by the liver, then the liver has tremendous metabolic capacity for the drug. In this case, flow of drug to the liver is what limits the metabolic rate. Metabolism is “flow limited.” The reduction in liver blood flow that accompanies anesthesia can be expected to reduce clearance. However, moderate changes in hepatic metabolic function per se will have little impact on clearance because hepatic metabolic capacity is overwhelmingly in excess of demand.

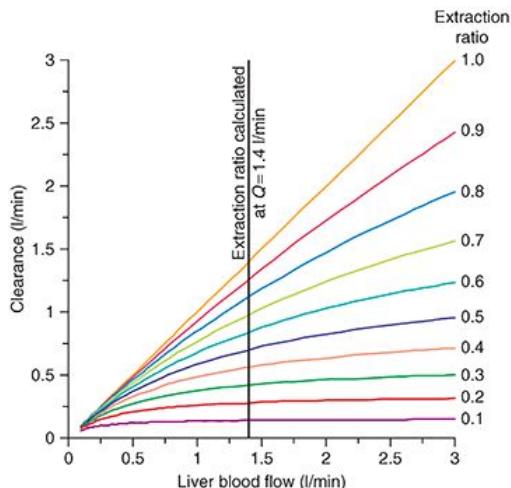


FIGURE 2.10 The relationship between liver blood flow (Q), clearance, and extraction ratio. For drugs with a high extraction ratio, clearance is nearly identical to liver blood flow. For drugs with a low extraction ratio, changes in liver blood flow have almost no effect on clearance. *Reprinted from Shafer SL, Flood P, Schwinn DA. Basic principles of pharmacology. In: Miller RD, Eriksson LI, Fleisher LA, Wiener-Kronish JP, Young WL, eds. Miller's Anesthesia. Vol 1. 7th ed. Philadelphia, PA: Churchill Livingstone; 2010:479-514.*

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Conversely, for drugs with an extraction ratio considerably less than 1, clearance is limited by the capacity of the liver to take up and metabolize the drug. This is called “capacity-limited” clearance. When clearance is capacity limited, changes in liver blood flow (as might be caused by the anesthetic state itself) have little influence on the clearance because the liver can only handle a fraction of the drug flowing through it. It does not matter if liver blood flow is doubled, or cut in half, because the liver’s enzymatic capacity is “maxed out” regardless of the amount of drug flowing through it.

When clearance is flow limited, it is generally unaffected by modest changes in hepatic capacity. However, when clearance is capacity limited, changes in liver metabolic capacity produce nearly proportional changes in clearance rate. For these drugs, clearance can be significantly decreased by hepatic disease or increased by enzymatic induction. This relationship can be seen in [Figure 2.11](#).

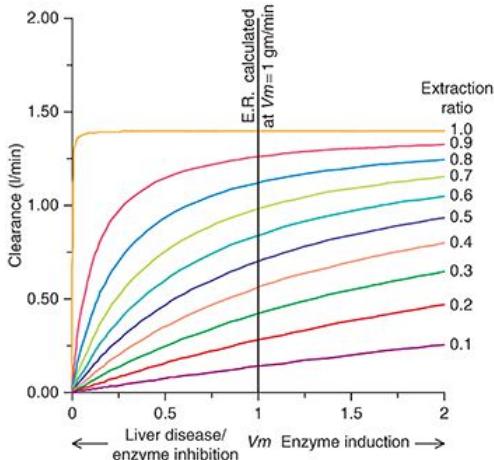


FIGURE 2.11 Changes in maximum metabolic velocity (V_m) have little effect on drugs with a high extraction ratio (ER) but cause a nearly proportional decrease in clearance for drugs with a low extraction ratio. Reprinted from Shafer SL, Flood P, Schwinn DA. Basic principles of pharmacology. In: Miller RD, Eriksson LI, Fleisher LA, Wiener-Kronish JP, Young WL, eds. Miller's Anesthesia. Vol 1. 7th ed. Philadelphia, PA: Churchill Livingstone; 2010:479-514. Copyright © 2010 Elsevier. With permission.

[Figure 2.11](#) allows us to also see how extraction ratio helps identify flow-limited from capacity-limited drugs. The vertical line at $V_m = 1$ shows the extraction ratio for each line (labeled to the left), based on a liver blood flow of 1.4 L per minute. Changes in V_m , as might be caused by liver disease (reduced V_m) or enzymatic induction (increased V_m) have little effect on drugs with a high extraction ratio. However, drugs with a low extraction ratio have a nearly linear change in clearance with a change in intrinsic metabolic capacity (V_m).

V_m and K_m are usually not known and condensed into a single term, $\frac{V_m}{K_m}$. This term summarizes the hepatic metabolic capacity and is called **intrinsic clearance**. Because $\text{clearance} = \frac{C_{\text{outflow}}}{C_{\text{inflow}}} \left(\frac{V_m}{K_m + C_{\text{outflow}}} \right)$, consider what happens if hepatic blood flow increases to infinity (this is a thought experiment—do not try this at home). At super high hepatic blood flow, C_{outflow} becomes indistinguishable from C_{inflow} because the finite hepatic capacity only metabolizes an infinitesimal fraction of the drug flowing through the liver. As a result, clearance becomes $\frac{V_m}{K_m + C_{\text{outflow}}} = \frac{V_m}{K_m}$. This is clearance when blood flow is infinitely fast. There must be a linear portion, where metabolism is proportional to concentration. We can solve for clearance in the “linear range” by solving for $C_{\text{inflow}} = C_{\text{outflow}} = 0$, $\frac{V_m}{K_m}$. This is the intrinsic clearance, Cl_{int} . It can be demonstrated algebraically from the definition of Cl_{int} that in the linear range (ie, when $K_m \gg C_{\text{outflow}}$), Cl_{int} is related to the extraction ratio and hepatic blood flow:

$$ER = \frac{Cl_{int}}{Q + Cl_{int}}$$

Equation 2.6

This relationship between intrinsic clearance and extraction ratio is shown in [Figure 2.12](#), calculated at a hepatic blood flow of 1,400 mL per minute. It shows that the intrinsic clearance for drugs like propofol with an extraction ratio of approximately 1 is enormous, somewhere around 100 L per minute!

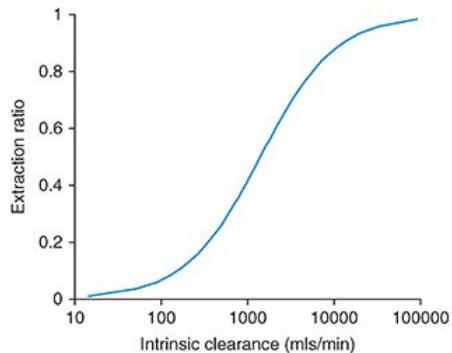


FIGURE 2.12 The extraction ratio as a function of the intrinsic calculated for a liver blood flow of 1,400 mL per minute. *Reprinted from Shafer SL, Flood P, Schwinn DA. Basic principles of pharmacology. In: Miller RD, Eriksson LI, Fleisher LA, Wiener-Kronish JP, Young WL, eds. Miller's Anesthesia. Vol 1. 7th ed. Philadelphia, PA: Churchill Livingstone; 2010:479-514. Copyright © 2010 Elsevier. With permission.*

Finally, we can combine [Equation 2.6](#) with [Equation 2.5](#) to solve for the relationship between hepatic clearance and Cl_{int} :

$$\text{Hepatic Clearance} = \frac{Q Cl_{int}}{Q + Cl_{int}}$$

Equation 2.7

In general, true hepatic clearance and extraction ratio are more useful concepts for anesthetic drugs than the intrinsic clearance. However, intrinsic clearance is introduced here because it is occasionally used in pharmacokinetic analyses of drugs used during anesthesia.

So far, we have focused on linear pharmacokinetics, that is, the pharmacokinetics of drugs whose metabolic rate at clinical doses is less than $Vm/3$. The clearance of such drugs is generally expressed as a constant (eg, propofol clearance = 1.6 L per minute). Some drugs, such as phenytoin, exhibit saturable pharmacokinetics (ie, have such low Vm that typical doses exceed the linear portion of [Figure 2.9](#)). The clearance of drugs with saturable metabolism is a function of drug concentration, rather than a constant flow (ie, volume per unit time). There are almost no drugs with saturable clearance in anesthesia, so they will not be discussed in greater detail. However, the clearance for these drugs as a function of concentration can be calculated from [Equations 2.5](#) and [2.7](#).

Renal Clearance

Renal excretion of drugs involves (1) glomerular filtration, (2) active tubular secretion, and (3) passive tubular reabsorption. The amount of drug that enters the renal tubular lumen depends on the fraction of drug bound to protein and the glomerular filtration rate (GFR). Renal tubular secretion involves active transport processes, which may be selective for certain drugs and metabolites, including protein-bound compounds. Reabsorption from renal tubules removes drug that has entered tubules by glomerular filtration and tubular secretion. This reabsorption is most prominent for lipid-soluble drugs that can easily cross cell membranes of renal tubular epithelial cells to enter pericapillary fluid. Indeed, a highly lipid-soluble drug, such as thiopental, is almost completely reabsorbed such that little or no unchanged drug is excreted in the urine. Conversely, production of less lipid-soluble metabolites limits renal tubule reabsorption and facilitates excretion in the urine.

The rate of reabsorption from renal tubules is influenced by factors such as pH and rate of urine flow in the renal tubules. Passive reabsorption of weak bases and acids is altered by urine pH, which influences the fraction of drug that exists in the ionized form. For example, weak acids are excreted more rapidly in alkaline urine. This occurs because alkalinization of the urine results in more ionized drug that cannot easily cross renal tubular epithelial cells, resulting in less passive reabsorption.

Renal blood flow is inversely correlated with age, as is creatinine clearance, which is closely related to GFR because creatinine is water-soluble and not resorbed in the tubules. Creatinine clearance can be predicted from age and weight according to the equation of Cockcroft and Gault⁹:

Men:

$$\text{Creatinine Clearance (mL/min)} = \frac{[140 - \text{age(years)}] \times \text{weight(kgs)}}{72 \times \text{serum creatinine (mg\%)}}$$

Women:

85% of the above equation.

Equation 2.8

[Equation 2.8](#) shows that age is an independent predictor of creatinine clearance. Elderly patients with normal serum creatinine have about half the GFR than younger patients. This can be seen graphically in [Figure 2.13](#).

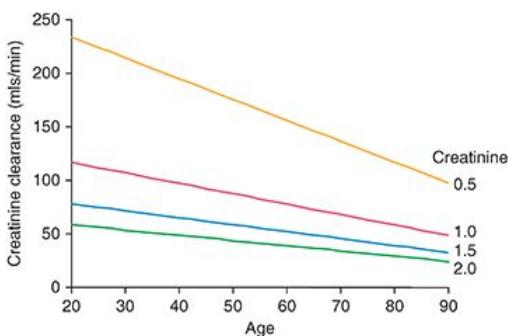


FIGURE 2.13 Creatinine clearance as a function of age and serum creatinine based on the equation of Cockcroft and Gault. *Derived from Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16:31-41.*

Absorption

Classically, pharmacokinetics is taught as “absorption, distribution, metabolism, and elimination.” Because most anesthetic drugs are administered intravenously, and inhaled anesthetic pharmacokinetics are discussed elsewhere, this order has been changed in this textbook to put absorption at the end of the list. Absorption is not particularly relevant for most anesthetic drugs.

Ionization

Most drugs are weak acids or bases that are present in both ionized and nonionized forms in solution. The nonionized molecule is usually lipid soluble and can diffuse across cell membranes including the blood–brain barrier, renal tubular epithelium, gastrointestinal epithelium, placenta, and hepatocytes ([Table 2.1](#)). As a result, it is usually the nonionized form of the drug that is pharmacologically active, undergoes reabsorption across renal tubules, is absorbed from the gastrointestinal tract, and is susceptible to hepatic metabolism. Conversely, the ionized fraction is poorly lipid soluble and cannot penetrate lipid cell membranes easily (see [Table 2.1](#)). A high degree of ionization thus impairs absorption of drug from the gastrointestinal tract, limits access to drug-metabolizing enzymes in the hepatocytes, and facilitates excretion of unchanged drug, as reabsorption across the renal tubular epithelium is unlikely.

TABLE 2.1

Characteristics of nonionized and ionized drug molecules

	Nonionized	Ionized
Pharmacologic effect	Active	Inactive

	Lipids	Water
Cross lipid barriers (gastrointestinal tract, blood–brain barrier, placenta)	Yes	No
Renal excretion	No	Yes
Hepatic metabolism	Yes	No

Determinants of Degree of Ionization

The degree of drug ionization is a function of its dissociation constant (pK) and the pH of the surrounding fluid. When the pK and the pH are identical, 50% of the drug exists in both the ionized and nonionized form. Small changes in pH can result in large changes in the extent of ionization, especially if the pH and pK values are similar. Acidic drugs, such as barbiturates, tend to be highly ionized at an alkaline pH, whereas basic drugs, such as opioids and local anesthetics, are highly ionized at an acid pH. Acidic drugs are usually supplied in a basic solution to make them more soluble in water and basic drugs are usually supplied in an acidic solution for the same reason, unless the pH affects drug stability, as is the case for most ester local anesthetics.

Ion Trapping

Because it is the nonionized drug that equilibrates across lipid membranes, a concentration difference of total drug can develop on two sides of a membrane that separates fluids with different pHs¹⁰ because the ionized concentrations will reflect the local equilibration between ionized and nonionized forms based on the pH. This is an important consideration because one fraction of the drug may be more pharmacologically active than the other fraction.

Systemic administration of a weak base, such as an opioid, can result in accumulation of ionized drug (ion trapping) in the acid environment of the stomach. A similar phenomenon occurs in the transfer of basic drugs, such as local anesthetics, across the placenta from mother to fetus because the fetal pH is lower than maternal pH. The lipid-soluble nonionized fraction of local anesthetic crosses the placenta and is converted to the poorly lipid-soluble ionized fraction in the more acidic environment of the fetus. The ionized fraction in the fetus cannot easily cross the placenta to the maternal circulation and thus is effectively trapped in the fetus. At the same time, conversion of the nonionized to ionized fraction maintains a gradient for continued passage of local anesthetic into the fetus. The resulting accumulation of local anesthetic in the fetus is accentuated by the acidosis that accompanies fetal distress.

The kidneys are the most important organs for the elimination of unchanged drugs or their metabolites. Water-soluble compounds are excreted more efficiently by the kidneys than are compounds with high lipid solubility. This emphasizes the important role of metabolism in converting lipid-soluble drugs to water-soluble metabolites. Drug elimination by the kidneys is correlated with endogenous creatinine clearance or serum creatinine concentration. The magnitude of change in these indices provides an estimate of the necessary change adjustment in drug dosage. Although age and many diseases are associated with a decrease in creatinine clearance and requirement for decreased dosing, pregnancy is associated with an increase in creatinine clearance and higher dose requirements for some drugs.

Ion trapping and extraction ratio featured, somewhat unexpectedly, in the trial of Conrad Murray for the death of Michael Jackson. The initial defense strategy was to blame Michael Jackson for his death, claiming that he drank a mixture of propofol and lidocaine when Conrad Murray stepped out of the room. We already know why the propofol claim is bogus. As discussed earlier, the extraction ratio for propofol is nearly 1. The extraction ratio does not care if the propofol enters the liver from the hepatic artery or portal vein. The liver will just as happily remove all the propofol from the portal vein as from the hepatic artery. As a result, any propofol that is swallowed will be metabolized in the liver before ever reaching the systemic circulation.

The defense also observed that the concentration of lidocaine in Michael Jackson's stomach was 22.9 $\mu\text{g}/\text{mL}$, far exceeding the concentration of lidocaine in Michael Jackson's blood of 0.8 $\mu\text{g}/\text{mL}$. Surely this was evidence that Michael Jackson drank a mixture of lidocaine and propofol! Nope. It is just ion trapping, nothing more.

We can quantitate the extent of ion trapping using the Henderson-Hasselbalch equation:

$$pH = pK_a + \log_{10} \left(\frac{[A^-]}{[HA]} \right)$$

Equation 2.9

This assumes that the dissociating moiety is an acid that releases a proton. However, lidocaine is a proton receptor, requiring we use the form of the Henderson-Hasselbalch equation adapted for bases:

$$pOH = pK_b + \log_{10} \left(\frac{[BH^+]}{[B]} \right)$$

Equation 2.10

where pOH is the negative logarithm (base 10) of the hydroxide ion concentration, pK_b is the base dissociation constant (readily calculated as $14 - pK_a$), $[B]$ is the concentration of the base (uncharged lidocaine), and $[BH^+]$ is the concentration of the conjugate acid (protonated lidocaine). We can rearrange the second equation to calculate the ratio of $[BH^+] / [B]$ as $10^{pOH - pK_b}$.

The pH of blood is 7.4, the pH of the stomach is 1 to 3.5, and the pK_a of lidocaine is 8.01. Therefore, the pOH of blood is 6.6, the pOH of the stomach is 10.5 to 13, and the pK_b of lidocaine is 5.99.

[Figure 2.14](#) was presented in pretrial testimony to explain the mathematics of ion trapping. The left shows blood, where the total lidocaine was measured on autopsy as 0.84 µg/mL. From the Henderson-Hasselbalch equation, we can calculate that the uncharged moiety was 0.17 µg/mL and the balance was charged. Because the uncharged moiety establishes equilibrium across gastric epithelium, we expect the lidocaine concentration in the stomach to be the same, 0.17 µg/mL. Knowing this, and the gastric pH, we can calculate the charged lidocaine concentration at equilibrium would have been 5,357 µg/mL, about 200 times higher than actually measured on autopsy. Of course, the system was not in equilibrium at the time of autopsy, which is why the stomach concentration was only 22.9 µg/mL, not 5,357 µg/mL. However, all that we know about Michael Jackson is that charged lidocaine accumulated in his stomach, exactly as expected from ion trapping.

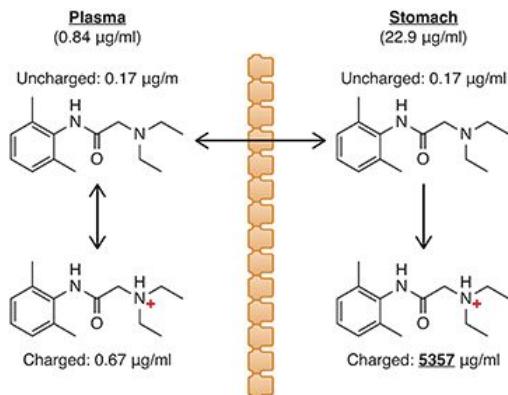


FIGURE 2.14 Ion trapping can result in significant sequestration of drugs based on local pH. The molecule shown is lidocaine, which has a nitrogen group that can accept protons in an acidic environment. Only neutrally charged lidocaine equilibrates across membranes. The figure is taken from the trial of Conrad Murray for the death of Michael Jackson. The defense claimed that the measured lidocaine concentration in the stomach, 22 µg/mL, proved that Mr. Jackson drank a mixture of lidocaine and propofol. However, the measured concentration can be entirely explained by ion trapping, which was not even close to the equilibrium concentration of 5,357 µg/mL.

Route of Administration and Systemic Absorption of Drugs

Drugs administered by intravenous injection or inhalation reach the systemic circulation almost instantly. However, for drugs not administered by these two routes, there is an initial delay between administering the

drug (eg, swallowing a pill or applying a patch) and appearance of the drug in the systemic circulation. The rate of systemic absorption determines the magnitude of the drug effect and duration of action. Changes in the rate of systemic absorption rate may require adjusting the dose or time interval between repeated drug doses.

Systemic absorption, regardless of the route of drug administration, depends on the drug's solubility. Local conditions at the site of absorption alter solubility, particularly in the gastrointestinal tract. Blood flow to the site of absorption also affects the rate of systemic transfer. For example, increased blood flow evoked by rubbing or applying heat at the subcutaneous or intramuscular injection site enhances systemic absorption, whereas decreased blood flow due to vasoconstriction impedes drug absorption. Finally, the area of the absorbing surface available for drug absorption is an important determinant of drug entry into the circulation.

Oral Administration

Oral administration of a drug is often the most convenient and inexpensive route of administration. Disadvantages of the oral route include (1) emesis caused by irritation of the gastrointestinal mucosa by the drug, (2) destruction of the drug by digestive enzymes or acidic gastric fluid, and (3) irregularities in absorption in the presence of food or other drugs. Furthermore, drugs may be metabolized by enzymes or bacteria in the gastrointestinal tract before systemic absorption can occur.

With oral administration, the onset of drug effect is largely determined by the rate and extent of absorption from the gastrointestinal tract. The principal site of most drug absorption after oral administration is the small intestine due to the large surface area of this portion of the gastrointestinal tract. Changes in the pH of gastrointestinal fluid that favor the presence of a drug in its nonionized (lipid-soluble) fraction thus favor systemic absorption. Some absorption occurs in the stomach, where the fluid is obviously acidic, enhancing the absorption of weak acids such as aspirin. However, most drug absorption occurs in the alkaline environment of the small intestine. The alkalinity enhances absorption of weak bases such as opioids, but even weak acids are mostly absorbed in the small intestine because of the large surface area.

First-Pass Hepatic Effect

Drugs absorbed from the gastrointestinal tract enter the portal venous blood and thus pass through the liver before entering the systemic circulation for delivery to tissue receptors. This is known as the **first-pass hepatic metabolism**. For drugs that undergo extensive hepatic extraction and metabolism (propranolol, lidocaine), it is the reason for large differences in the pharmacologic effect between oral and intravenous doses. As mentioned earlier, it is also the reason that propofol exerts no pharmacologic effect when swallowed—none gets past the liver.

Sublingual, Buccal, and Nasal Administration

The sublingual or buccal route of administration permits a rapid onset of drug effect because this blood bypasses the liver, preventing first-pass metabolism for the initial dose. Drugs absorbed from the oral cavity flow into the superior vena cava. Evidence of the value of bypassing the first-pass hepatic effect is the efficacy of sublingual nitroglycerin. Sublingual nitroglycerin works quickly, while oral nitroglycerin tablets are ineffective because of extensive first-pass hepatic metabolism. It is also why oral transmucosal fentanyl citrate results in a rapid rise in fentanyl concentration for “breakthrough” cancer pain where rapid onset of pain relief is clinically important. Oral fentanyl has an extraction ratio of about 50%, which greatly limits the utility of oral administration. Buccal administration is an alternative to sublingual placement of a drug; it is better tolerated and less likely to stimulate salivation. Buccal buprenorphine is an example of effective buccal administration.

The nasal mucosa also provides an effective absorption surface for certain drugs. For example, in 2019, the US Food and Drug Administration approved nasally administered s-ketamine for treatment resistant depression. Nasally administered naloxone is now widely available to emergency medical technicians for treatment of opioid overdose. The nasal route affords very rapid reversal of opioid overdose.

Transdermal Administration

Transdermal administration of drugs provides sustained therapeutic plasma concentrations of the drug and decreases the likelihood of loss of therapeutic efficacy due to peaks and valleys associated with conventional intermittent drug injections. This route of administration is devoid of the complexity of continuous infusion techniques, and the low incidence of side effects (because of the small doses used) contributes to high patient compliance. Characteristics of drugs that favor predictable transdermal absorption include (1) combined water and lipid solubility, (2) molecular weight of <1,000, (3) pH 5 to 9 in a saturated aqueous solution, (4) absence of histamine-releasing effects, and (5) daily dose requirements of <10 mg. Scopolamine, fentanyl, clonidine, estrogen, progesterone, and nitroglycerin can be delivered with commercially approved transdermal systems. For some drugs, such as scopolamine and nitroglycerine, the sustained plasma concentrations provided by transdermal absorption result in tolerance and loss of therapeutic effect.

The rate-limiting step in transdermal absorption of drugs is diffusion across the stratum corneum of the epidermis. Initial absorption occurs along sweat ducts and hair follicles that function as diffusion shunts. Differences in the thickness and chemistry of the stratum corneum are reflected in the skin's permeability to drug absorption. For example, skin may be 10 to 20 micron thick on the back and abdomen compared with 400 to 600 micron on the palmar surfaces of the hands. This explains part of the variability in transdermal delivery. This is the reason that scopolamine patches are placed behind the ear. It has nothing to do with the proximity to the semicircular canals. The postauricular zone, because of its thin epidermal layer and somewhat higher temperature, is the only region of skin sufficiently permeable for predictable and sustained absorption of scopolamine.

The stratum corneum sloughs and regenerates over about 7 days, placing an upper limit on the adhesion duration of transdermal delivery systems. Contact dermatitis at the site of transdermal patch applications occurs in a significant number of patients and is another reason to limit the duration of patch placement.

Rectal Administration

Drugs administered into the proximal rectum are absorbed into the superior hemorrhoidal veins and subsequently transported via the portal venous system to the liver. Thus, rectally administered drugs undergo the same first pass metabolism as orally administered drugs. However, if the drugs are placed more distal (eg, closer to the anus), then they may be absorbed directly into the systemic circulation, bypassing the liver. This is one of the reasons that rectal drug delivery is exceptionally unpredictable. Furthermore, drugs may cause irritation of the rectal mucosa. Patients have limited enthusiasm for this route of drug delivery.

Pharmacokinetic Models

In the following section, several common, useful pharmacokinetic models are derived. Although it is not necessary for every clinician to be able to derive these models, a consideration of where they come from takes them out of the "black box" and allows consideration of their representative parts.

Zero- and First-Order Processes

The consumption of oxygen and production of carbon dioxide are processes that happen at a constant rate.

These are called **zero-order processes**. The rate of change (dx/dt) for a zero-order process is $\frac{dx}{dt} = k$. This says the rate of change is constant. If x represents an amount of drug and t represents time, then the units of k are amount/time. If we want to know the value of x at time t , $x(t)$, we can compute it as the integral of this equation from time 0 to time t : $x(t) = x_0 + k \cdot t$, where x_0 is the value of x at time 0. This is the equation of a straight line with a slope of k and an intercept of x_0 .

Many processes occur at a rate proportional to the amount. For example, the interest payment on a loan is proportional to the outstanding balance. The rate at which water drains from a bathtub is proportional to amount (height) of water in the tub. These are examples of first-order processes. The rate of change in a first-

order process is only slightly more complex than for a zero-order process, $\frac{dx}{dt} = k \cdot x$. In this equation, x has units of amount, so the units of k are 1/time. The value of x at time t , $x(t)$, can be computed as the integral from time 0 to time t : $x(t) = x_0 e^{kt}$, where x_0 is the value of x at time 0. If $k > 0$, $x(t)$ increases exponentially to

infinity. If $k < 0$, $x(t)$ decreases exponentially to 0. In pharmacokinetics, k is negative because concentrations decrease over time. For clarity, the minus sign is usually explicit, so k is expressed as a positive number. Thus, the identical equation for pharmacokinetics, with the minus sign explicitly written, is

$$x(t) = x_0 e^{-kt}$$

Equation 2.11

Figure 2.15A shows the exponential relationship between x and time. X continuously decreases over time. Taking the natural logarithm of both sides of $x(t) = x_0 e^{-kt}$ gives

$$\begin{aligned}\ln[x(t)] &= \ln(x_0 \cdot e^{-kt}) \\ &= \ln(x_0) + \ln(e^{-kt}) \\ &= \ln(x_0) - k \cdot t\end{aligned}$$

Equation 2.12

This is the equation of a straight line, as shown in **Figure 2.15B**, where the vertical axis is $\ln[x(t)]$, the horizontal axis is t , the intercept is $\ln(x_0)$, and the slope of the line is $-k$. How long will it take for x to go from some value, x_1 , to half that value, $x_{1/2}$? Because k is the slope of a straight line relating $\ln(x)$ to time, it follows that

$$k = \frac{\Delta \ln(x)}{\Delta t} = \frac{\ln(x) - \ln\left(\frac{x}{2}\right)}{t_{1/2}} = \frac{\ln\left(\frac{x}{\left(\frac{x}{2}\right)}\right)}{t_{1/2}} = \frac{\ln(2)}{t_{1/2}} \approx \frac{0.693}{t_{1/2}}$$

Equation 2.13

where $t_{1/2}$ is the “half-life,” the time required for a 50% decrease in x . The natural log of 2 is close enough to 0.693 to be considered an equality in subsequent equations here.

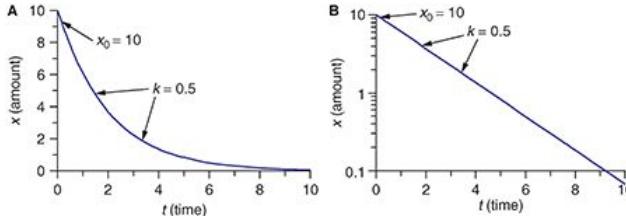


FIGURE 2.15 Exponential decay curve, as given by $x(t) = x_0 e^{-kt}$, plotted on standard axis (A) and a logarithmic axis (B).

Thus, the relationship of the slope (or “rate constant”), k , to half-life, $t_{1/2}$ is $k = \frac{0.693}{t_{1/2}}$. If we measure the time it takes for x to fall by 50%, $t_{1/2}$, then we know the rate constant, k . Conversely, if we know k , the rate constant, we can easily calculate the time it will take for x to fall by 50% as

$$t_{1/2} = \frac{0.693}{k}$$

Equation 2.14

Physiologic Pharmacokinetic Models

It is possible to analyze volumes and clearances for each organ in the body and construct models of pharmacokinetics by assembling the organ models into physiologically and anatomically accurate models of the entire animal. **Figure 2.16** shows such a model for thiopental in rats.¹¹ However, models that work with individual tissues are mathematically cumbersome and do not offer a better prediction of plasma drug

concentration than models that lump the tissues into a few compartments. If the goal is to determine how to give drugs in order to obtain therapeutic plasma drug concentrations, then all that is needed is to mathematically relate dose to plasma concentration. For this purpose, “compartmental” models are usually adequate.

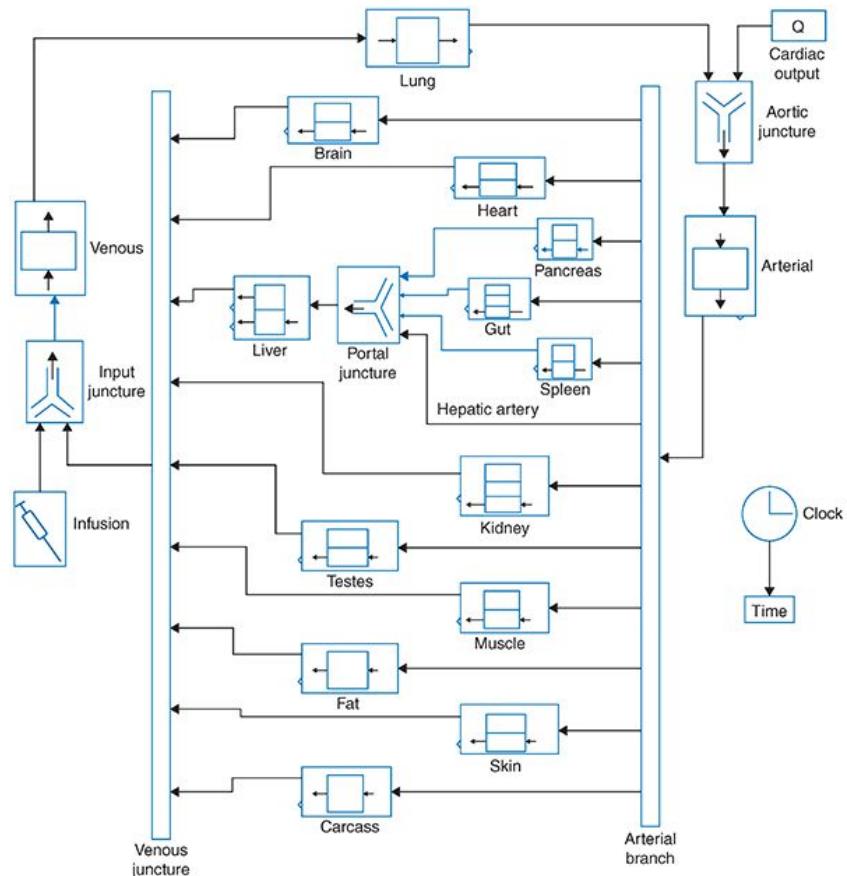


FIGURE 2.16 Physiologic model for thiopental in rats. The pharmacokinetics of distribution into each organ has been individually determined. The components of the model are linked by zero-order (flow) and first-order (diffusion) processes. Reprinted by permission from Springer: Ebling WF, Wada DR, Stanski DR. From piecewise to full physiologic pharmacokinetic modeling: applied to thiopental disposition in the rat. J Pharmacokinetic Biopharm. 1994;22(4):259-292. Copyright © 1994 Plenum Publishing Corporation.

Compartmental Pharmacokinetic Models

Compartmental models are built on the same basic concepts as physiologic models. The “one-compartment model” ([Figure 2.17A](#)) contains a single volume and a single clearance, as though we were buckets of fluid. For anesthetic drugs, we resemble several buckets connected by pipes. These are usually modeled using two- or three-compartment models ([Figure 2.17B,C](#)). The volume to the left in the two-compartment model and in the center of the three-compartment model is the central volume. This is the volume where we inject our intravenous drugs and also the volume we measure when we draw blood samples. The other volumes are peripheral volumes of distribution. The sum of the all volumes is the volume of distribution at steady state, Vd_{ss} . The clearance for drugs permanently removed from the central compartment is the “systemic clearance,” so named because it is the process that clears drug from the entire system. The clearances between the central compartment and the peripheral compartments are the “intercompartmental” clearances. Although the concept of compartments yields useful mathematics for planning dosing, when experimental animals were flash frozen at different times following administration of anesthetic drugs, and characterized

using physiologic models, none of the compartments identified in two and three compartment models could be anatomically identified.¹² Other than clearance, none of the parameters of compartment models readily translates into any anatomic structure or physiologic process.

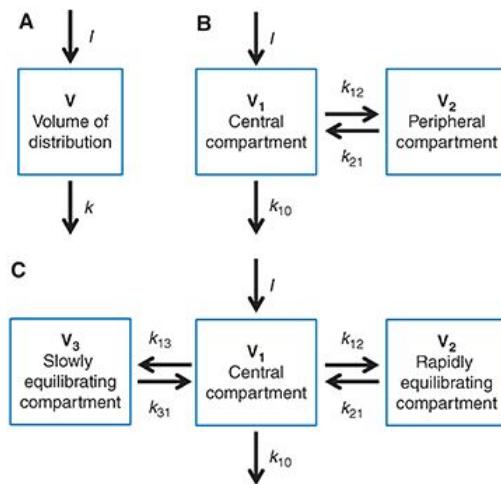


FIGURE 2.17 Standard one- (A), two- (B), and three-compartment (C) mammillary pharmacokinetic models. I represents any input into the system (eg, bolus or infusion). The volumes are represented by V and the rate constants by k . The subscripts on rate constants indicate the direction of flow, noted as $k_{\text{from to}}$.

One-Compartment Model

Bolus Pharmacokinetics

Returning to the one-compartment bucket, let us call the amount of drug poured into the bucket x_0 (x at time 0).

Remembering that the definition of concentration is amount divided by volume, by definition concentration immediately following a bolus dose, C_0 is:

$$C_0 = x_0/V$$

Equation 2.15

where x_0 is the amount at time 0 (i.e., the amount of the bolus dose) and V is the volume of the compartment. We can rearrange equation 2.15 to calculate the bolus dose for any desired target concentration, C_T :

$$\text{Dose} = C_T \times V$$

Equation 2.16

Let us assume that the fluid is being drained through a pipe at a constant rate, which we will call **clearance**, Cl . What is the rate, dx/dt , that drug x is leaving the bucket? It is the concentration of drug times the rate of flow through the pipe:

$$\frac{dx}{dt} = \text{Concentration} \cdot Cl = \frac{x}{V} \cdot Cl = x \cdot \frac{Cl}{V}$$

Equation 2.17

We will come back to this equation many times.

Because Cl/V is a constant, and the rate $x \times Cl/V$ is obviously proportional to x , $\frac{dx}{dt}$ is a first-order process. We know that a first order process can be expressed as $\frac{dx}{dt} = k x$. Since $\frac{dx}{dt} = x \frac{Cl}{V} = k x$, it follows that $k = \frac{Cl}{V}$. This can be rearranged to yield a fundamental identity of linear pharmacokinetics:

$$Cl = k \times V$$

Equation 2.18

What does this identity tell us about the relationship between half-life, volume, and clearance? Rearranging the above equation as $k = \frac{Cl}{V}$ and remembering that $t_{1/2} = \frac{0.693}{k}$, we can conclude that half-life is proportional to volume and inversely proportional to clearance.

$$t_{1/2} = 0.693 \frac{V}{Cl}$$

Equation 2.19

Consider two alternative models, one with a large volume and a small clearance ([Figure 2.18A](#)), and one with a small volume and a large clearance ([Figure 2.18B](#)). It is (hopefully) intuitively obvious that following bolus injection, concentrations will fall more quickly (shorter half-life) with the larger clearance and smaller volume as predicted by [Equation 2.16](#) and shown in [figure 2.18B](#).

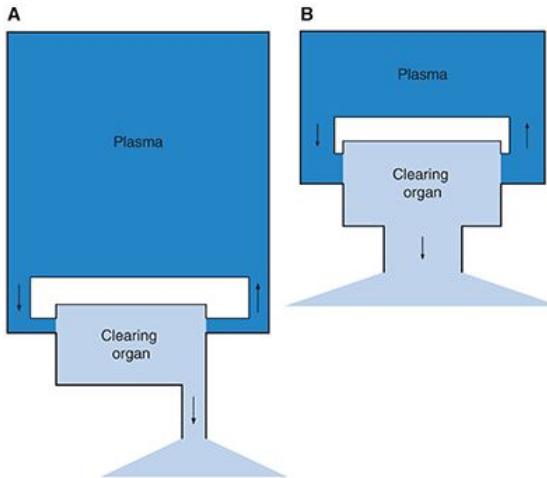


FIGURE 2.18 The relationship between volume and clearance and half-life can be envisioned by considering two settings: a big volume and a small clearance (A) and a small volume with a big clearance (B). Drug will be eliminated faster in the latter case.

Because this is a first-order process, let us calculate the concentration of drug that remains in the bucket as drug is being cleared following bolus injection. Using the equation that describes first-order processes, $x(t) = x_0 e^{-kt}$, $x(t)$ is the amount of drug at time t , x_0 is the amount of drug right after bolus injection, and k is the rate constant (Cl/V). If we divide both sides by V , and remember that x/V is the definition of concentration, we get the equation that relates concentration following an intravenous bolus to time and initial concentration:

$$C(t) = C_0 e^{-kt}$$

Equation 2.20

This equation defines the “concentration over time” curve for a one-compartment model after a bolus of drug and has the log linear shape seen in [Figure 2.15B](#).

In a typical experiment, we start with the concentrations, as seen in [Figure 2.15](#), and calculate clearance in one of two ways. First, we can calculate V by rearranging the definition of concentration, $V = \text{dose}/\text{initial concentration} = \text{dose}/C_0$. If you know the dose and you measure C_0 in the experiment, you can calculate V . If you then fit the log (C) line versus time line to a straight line, you can directly measure the slope, $-k$. You can then calculate clearance as $k \cdot V$.

A more general solution is to consider the integral of the concentration over time curve, $C(t) = C_0 e^{-kt}$, known in pharmacokinetics as the area under the curve, or AUC:

$$\begin{aligned} AUC &= \int_0^{\infty} C_0 e^{-kt} dt \\ &= \int_0^{\infty} \frac{x_0}{V} \left(e^{-\frac{Cl}{V}t} \right) dt \text{ (substituting for } C_0 \text{ and } k) \\ &= \frac{x_0}{V} \times \frac{V}{Cl} \text{ (evaluating the above integral)} \\ &= \frac{x_0}{Cl} \end{aligned}$$

Equation 2.21

We can rearrange the right side and the last term on the left side to solve for clearance, Cl :

$$Cl = \frac{x_0}{AUC}$$

Equation 2.22

Because x_0 is the dose of drug, clearance equals the dose divided by the AUC. This fundamental property of *linear* pharmacokinetic models applies to one-compartment models, to multicompartment models, and to any type of intravenous drug dosing (provided the *total* dose administered is used as the numerator). It directly follows that AUC is proportional to dose for linear models (ie, models where Cl is constant).

The term *linear pharmacokinetics* has been used multiple times, starting with [Figure 2.9](#) showing that in the “linear” portion, metabolism was clearly proportional to concentrations. Now that the basic concepts have been introduced, we can define “linear” more precisely. If metabolism is proportional to concentration, as

seen in [Figure 2.9](#), then metabolism, defined as $\frac{dx}{dt}$ is therefore a first-order process defined by a rate constant $k = \frac{Cl}{V}$. Since k is constant, and V is constant, then clearance, Cl , must also be constant. In other words, clearance does not change with dose, concentration, time, or anything else. When clearance is constant, the pharmacokinetics are said to be “linear” because a linear (eg, proportional) increase in dose results in a linear (eg, proportional) increase in concentration. More intuitively stated, if you double the dose, you double the concentration. It also means that if you give a dose now, and another dose in an hour, the concentrations after the second dose what you would expect from the second dose alone, “linearly” added to the residual concentrations from the first dose. This is also called the principle of superposition.

Occasionally the term *linear* is confusing because the curves of concentration over time are typically exponentially increasing or decreasing rather than straight lines. That is not what linear implies because concentrations over time are virtually never straight lines. Linear pharmacokinetics are “linear” with respect to *dose*, but never with respect to time.

Infusion Pharmacokinetics

If you give an infusion at a rate of I (for *Input*), the plasma concentration will rise as long as the rate of drug going into the body, I , exceeds the rate at which drug leaves the body, $C \cdot Cl$, where C is the drug concentration. Once, $I = C \cdot Cl$, drug is going in and coming out at the same rate, and the body is at steady

state. We can calculate the concentration at steady state by observing that the rate of drug going in must equal the rate of drug coming out. At steady state, the drug concentration is C_{ss} . Based on [Equation 2.17](#), drug is leaving the system at the rate $C_{ss} \cdot Cl$. Because at steady state, the infusion rate equals the metabolic rate, the infusion rate, I , must therefore equal the metabolic rate, $C_{ss} \cdot Cl$.

This can be rearranged to give the concentration of drug at steady state during an infusion:

$$C_{ss} = \frac{I}{Cl}$$

Equation 2.23

Thus, the steady-state concentration during an infusion is the rate of drug input divided by the clearance. It follows that if we want to calculate the infusion rate that will achieve a given target concentration, C_T , at steady state, then the infusion rate must be $C_T \cdot Cl$.

$C_{ss} \cdot \frac{I}{Cl}$ is similar in form to the equation describing the concentration following a bolus injection: $C_0 = \frac{x_0}{V}$ as shown in [equation 2.15](#). Thus, volume is a scalar relating bolus dose to initial concentration, and clearance is a scalar relating infusion rate to steady-state concentration. It follows that the initial concentration following a bolus is independent of the clearance, and the steady-state concentration during a continuous infusion is independent of the volume.

During an infusion, the rate of change in the amount of drug, x , is rate of inflow, I , minus the rate of outflow, $k \cdot x$, which is represented as $\frac{dx}{dt} = I - kx$. We can calculate x at any time t as the integral from time 0 to time t . Assuming that we are starting with no drug in the body (ie, $x_0 = 0$), the result is $x(t) = \frac{I}{k}(1 - e^{-kt})$. If we divide both sides by volume, V , and remember that $Cl = k \cdot V$, we can solve this equation for concentration: $C(t) = \frac{I}{Cl}(1 - e^{-kt})$. This is the equation for concentration during an infusion in a one-compartment model.

As $t \rightarrow \infty$, $e^{-kt} \rightarrow 0$, the equation $x(t) = \frac{I}{k}(1 - e^{-kt})$ reduces to $x_{ss} = \frac{I}{k}$. During an infusion, the amount in the body approaches x_{ss} (steady state) asymptotically, only reaching it at infinity. However, we can calculate how

long it takes to get to half of the steady-state amount, $\frac{x_{ss}}{2}$. If $x_{ss} = \frac{I}{k}$, then $\frac{x_{ss}}{2} = \frac{I}{2k}$. Because $\frac{I}{2k}$ is the amount of drug when we are halfway to steady state, we can substitute that for the amount of drug in our formula, $x(t) = \frac{I}{k}(1 - e^{-kt})$, giving us $\frac{I}{2k} = \frac{I}{k}(1 - e^{-kt})$, and solve that for t . The solution is $t_{1/2} = \frac{\ln(2)}{k}$. This is the time to rise to half of the steady state concentration. Recall that $t_{1/2}$, the half time to decrease to 0 following a bolus

injection, was $\frac{\ln(2)}{k}$. We again have a parallel between boluses and infusions. Following a bolus, it takes 1 half-life to reduce the concentrations by half, and during an infusion, it takes 1 half-life to increase the concentration halfway to steady state. Similarly, it takes 2 half-lives to reach 75%, 3 half-lives to reach 87.5%, and 5 half-lives to reach 97% of the steady-state concentration. By 4 to 5 half-lives, we typically consider the patient to be at steady state, although the concentrations only asymptotically approach the steady-state value.

Absorption Pharmacokinetics

When drugs are given intravenously, every molecule reaches the systemic circulation. When drugs are given by a different route, such as orally, transdermally, or intramuscularly, the drug must first reach the systemic circulation. Oral drugs may be only partly absorbed. What is absorbed then has to get past the liver (“first-pass hepatic metabolism”) before reaching the systemic circulation. Transdermally applied drugs may be rubbed off, removed with soap or alcohol, or be sloughed off with the stratum corneum without being

absorbed. The dose of drug that eventually reaches the systemic circulation with alternative routes of drug delivery is the administered dose times f , the fraction “bioavailable.”

Alternative routes of drug delivery are often modeled by assuming the drug is absorbed from a reservoir or depot, usually modeled as an additional compartment with a monoexponential rate of transfer to the systemic circulation, $A(t) = f \cdot D_{\text{oral}} \cdot k_a \cdot e^{-k_a t}$, where $A(t)$ is the absorption rate at time t , f is the fraction bioavailable, D_{oral} is the dose taken orally (or intramuscularly, applied to the skin, etc). The k_a is the absorption rate constant. Because the integral of $e^{-k_a t}$ is 1, the total amount of drug absorbed is $f \cdot D_{\text{oral}}$. To compute the concentrations over time, we first reduce the problem to differential equations and integrate. The differential equation for the amount, x , with oral absorption into a one-compartment disposition model is

$$\frac{dx}{dt} = \text{inflow} - \text{outflow} = A(t) - k \cdot x = \\ f \cdot D_{\text{oral}} \cdot k_a \cdot e^{-k_a t} - k \cdot x$$

Equation 2.24

This is simply the rate of absorption at time t , $A(t)$, minus the rate of exit, $k \cdot x$. The amount of drug, x , in the compartment at time t is the integral of this from 0 to time t :

$$x(t) = \frac{D_{\text{oral}} f k_a}{k - k_a} (e^{-k_a t} - e^{-kt})$$

Equation 2.25

This equation describes the amount of drug in the systemic circulation following first-order absorption from a depot, such as the stomach, an intramuscular injection, the skin, or even an epidural dose. To describe the concentrations, rather than amounts of drug, it is necessary to divide both sides by V , the volume of distribution.

Multicompartment Models

The previous section used one-compartment model to introduce concepts of rate constants and half-lives and relate them to the physiologic concepts of volume and clearance. Unfortunately, none of the drugs used in anesthesia can be accurately characterized by one-compartment models because anesthetic drugs distribute extensively into peripheral tissues. To describe the pharmacokinetics of intravenous anesthetics, we must extend the one-compartment model to account for this distribution.

The plasma concentrations over time following an intravenous bolus resemble the curve in [Figure 2.19](#). In contrast to [Figure 2.15](#), [Figure 2.19](#) is not a straight line even though it is plotted on a log y-axis. This curve has the characteristics common to most drugs when given by intravenous bolus. First, the concentrations continuously decrease over time. Second, the rate of decline is initially steep but becomes less steep over time until we get to a portion that is “log-linear.”

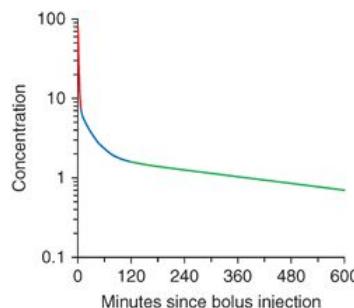


FIGURE 2.19 Typical time course of plasma concentration following bolus injection of an intravenous drug, with a rapid phase (red), an intermediate phase (blue), and a slow log-linear phase (green). The simulation was performed with the pharmacokinetics of fentanyl. *Reprinted with permission from Scott JC,*

Stanski DR. Decreased fentanyl and alfentanil dose requirements with age. A simultaneous pharmacokinetic and pharmacodynamics evaluation. J Pharmacol Exp Ther. 1987;240(1):159-166. Copyright © 1987 by The American Society for Pharmacology and Experimental Therapeutics.

Many anesthetic drugs appear to have three distinct phases, as suggested by [Figure 2.19](#). There is a “rapid distribution” phase (red in [Figure 2.19](#)) that begins immediately after bolus injection. Very rapid movement of the drug from the plasma to the rapidly equilibrating tissues characterizes this phase. Often, there is a second “slow distribution” phase (blue in [Figure 2.19](#)) that is characterized by movement of drug into more slowly equilibrating tissues and return of drug to the plasma from the most rapidly equilibrating tissues. The terminal phase (green in [Figure 2.19](#)) is a straight line when plotted on a semilogarithmic graph. The distinguishing characteristic of the terminal elimination phase is that the plasma concentration is lower than the tissue concentrations, and the relative proportion of drug in the plasma and peripheral volumes of distribution remains constant. During this “terminal phase,” drug returns from the rapid and slow distribution volumes to the plasma and is permanently removed from the plasma by metabolism or excretion.

The presence of three distinct phases following bolus injection is a defining characteristic of a mammillary model with three compartments. (A mammillary model consists of a central compartment with peripheral compartments connecting to it. There are no interconnections among other compartments.) It is possible to develop “hydraulic” models, as shown in [Figure 2.20](#), for intravenous drugs.¹³ In this model, there are three tanks, corresponding (from left to right) with the slowly equilibrating peripheral compartment, the central compartment (the plasma, into which drug is injected), and the rapidly equilibrating peripheral compartment. The horizontal pipes represent intercompartmental clearance or (for the pipe draining onto the page) metabolic clearance. The volumes of each tank correspond with the volumes of the compartments for fentanyl. The cross-sectional areas of the pipes correlate with fentanyl systemic and intercompartmental clearances. The height of water in each tank corresponds to drug concentration.

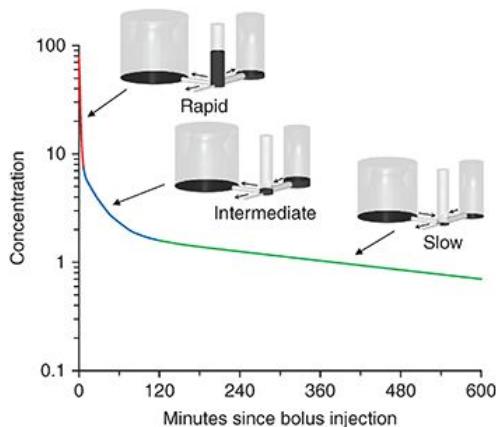


FIGURE 2.20 Hydraulic equivalent of the model in [Figure 2.19](#). Adapted with permission from Youngs EJ, Shafer SL. Basic pharmacokinetic and pharmacodynamic principles. In: White PF, ed. Textbook of Intravenous Anesthesia. Baltimore, MD: Lippincott Williams & Wilkins; 1997:10.

We can follow the processes that decrease drug concentration over time following bolus injection. Initially, drug flows from the central compartment to both peripheral compartments and is eliminated via the drain pipe through metabolic clearance. Because there are three places for drug to go, the central compartment concentration decreases very rapidly. At the transition between the red and the blue lines, there is a change in the role of the most rapidly equilibrating compartment. At this transition, the central compartment concentration falls below the concentration in the rapidly equilibrating compartment, and the direction of flow between them is reversed. After this transition (blue line), drug in the plasma only has two places to go: the slowly equilibrating compartment or out the drain pipe. These processes are partly offset by the return of drug to the plasma from the rapidly equilibrating compartment, which slows the decrease in plasma concentration. Once the concentration in the central compartment falls below both the rapidly and

slowly equilibrating compartments (*green line*), then the only method of decreasing the plasma concentration is clearance out the drain pipe. Drug accumulated in the rapidly and slowly equilibrating compartments acts as an enormous drag on the system, and the little drain pipe now is working against the entire body store of drug.

Curves that continuously decrease over time, with a continuously increasing slope (ie, curves that look like [Figures 2.19](#) and [2.20](#)), can be described by a sum of negative exponentials, as shown in [Figure 2.21](#), which shows how three single exponential curves are added together to get a sum of exponentials that describes the plasma concentrations over time after bolus injection:

$$C(t) = Ae^{-\alpha t} + Be^{-\beta t} + Ce^{-\gamma t}$$

Equation 2.26

where t is the time since the bolus; $C(t)$ is the drug concentration following a bolus dose; and A , α , B , β , C , and γ are parameters of a pharmacokinetic model. A , B , and C are called **coefficients**, whereas α , β , and γ are called **exponents**. Following a bolus injection, all six of the parameters (A , α , B , β , C , and γ) will be greater than 0.

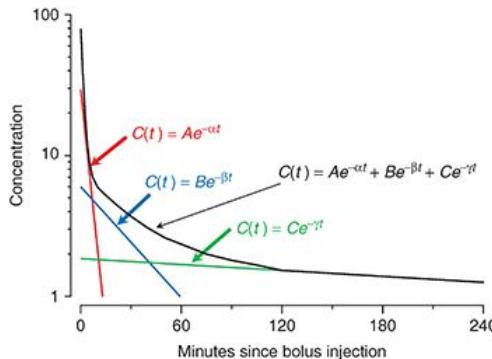


FIGURE 2.21 The polyexponential equation that describes the decline in plasma concentration for most intravenous anesthetics is the algebraic sum of the exponential terms that represent rapid phase shown in red, intermediate phase shown in blue and slow phase shown in green.

The main reason that polyexponential equations are used is that they work. These equations describe reasonably accurately the plasma concentrations observed after bolus injection, except for the misspecification in the first few minutes mentioned previously.

Polyexponential equations permit us to use the one-compartment ideas just developed, with some generalization of the concepts. $C(t) = Ae^{-\alpha t} + Be^{-\beta t} + Ce^{-\gamma t}$ says that the concentrations over time are the algebraic sum of three separate functions, $Ae^{-\alpha t}$, $Be^{-\beta t}$, and $Ce^{-\gamma t}$. Typically, $\alpha > \beta > \gamma$ by about 1 order of magnitude. At time 0 ($t = 0$), [Equation 2.22](#) reduces to $C_0 = A + B + C$. In other words, the sum of the coefficients A , B , and C equals the concentration immediately following a bolus. It thus follows that $A + B + C = \text{bolus amount} / V_1$.

Constructing pharmacokinetic models represents a trade-off between accurately describing the data, having confidence in the results, and mathematical tractability. Adding exponents to the model usually provides a better description of the observed concentrations. However, adding more exponent terms usually decreases our confidence in how well we know each coefficient and exponential and *greatly* increases the mathematical burden of the models. This is why most pharmacokinetic models are limited to two or three exponents.

Polyexponential models can be mathematically transformed from the admittedly unintuitive exponential form $C(t) = Ae^{-\alpha t} + Be^{-\beta t} + Ce^{-\gamma t}$ to a more easily visualized compartmental form, as shown in [Figures 2.17](#) and [2.20](#). Micro-rate constants, expressed as k_{ij} , define the rate of drug transfer from compartment i to

compartment j. Compartment 0 is the compartment outside the model, so k_{10} is the micro-rate constant for irreversible removal of drug from the central compartment (analogous to k for a one-compartment model).

The intercompartmental micro-rate constants (k_{12} , k_{21} , etc) describe the movement of drug between the central and peripheral compartments. Each peripheral compartment has two micro-rate constants, one for drug entry and one for drug exit. The micro-rate constants for the two- and three-compartment models can be seen in [Figure 2.17](#). The differential equations describing the rate of change for the amount of drug in compartments 1, 2, and 3 follow directly from the micro-rate constants. For the two-compartment model, the differential equations for each compartment are as follows:

$$\begin{aligned}\frac{dx_1}{dt} &= I + x_2 k_{21} - x_1 k_{10} - x_1 k_{12} \\ \frac{dx_2}{dt} &= x_1 k_{12} - x_2 k_{21}\end{aligned}$$

Equation 2.27

where I is the rate of drug input. For the three-compartment model, the differential equations for each compartment are as follows:

$$\begin{aligned}\frac{dx_1}{dt} &= I + x_3 k_{31} + x_2 k_{21} - x_1 k_{10} - x_1 k_{12} - x_1 k_{13} \\ \frac{dx_2}{dt} &= x_1 k_{12} - x_2 k_{21} \\ \frac{dx_3}{dt} &= x_1 k_{13} - x_3 k_{31}\end{aligned}$$

Equation 2.28

For the one-compartment model, k was both the rate constant and the exponent. For multicompartment models, the relationships are more complex. The interconversion between the micro-rate constants and the exponents becomes exceedingly complex as more exponents are added because every exponent is a function of every micro-rate constant and vice versa. Individuals interested in such interconversions can find them in the Excel spreadsheet “convert.xls,” which can be downloaded from <https://github.com/StevenLShafer/Pharmacokinetics/blob/master/convert.xls>. This is useful because publications on pharmacokinetics may use one or another system, and it is difficult to compare without converting the exponents to micro-rate constants.

The Time Course of Drug Effect

The plasma is not the site of drug effect for anesthetic drugs. There is a time lag between plasma drug concentration and effect site drug concentration. Consider the different rate of onset for fentanyl and alfentanil. [Figure 2.21](#) is from work by Stanski and colleagues.^{14,15} The black bar in [Figure 2.22A](#) shows the duration of a fentanyl infusion.¹⁴ Rapid arterial samples document the rise in fentanyl concentration. The time course of electroencephalogram effect (spectral edge) lags 2 to 3 minutes behind the rapid rise in arterial concentration. This lag is called **hysteresis**. The plasma concentration peaks at the moment the infusion is turned off. Following the peak plasma concentration (and the Disney logo that appears at peak plasma concentration), the plasma fentanyl concentration rapidly decreases. However, the offset of fentanyl drug effect lags well behind the decrease in plasma concentration. [Figure 2.22B](#) shows the same study design in a patient receiving alfentanil. Because of alfentanil’s rapid blood–brain equilibration, there is less hysteresis (delay) with alfentanil than with fentanyl.

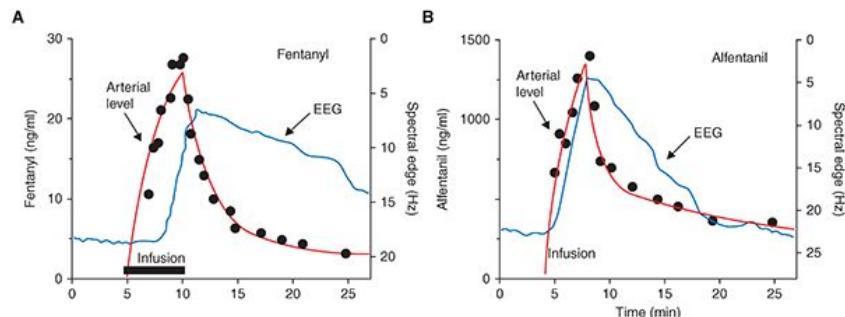


FIGURE 2.22 Fentanyl and alfentanil arterial concentrations (circles) and electroencephalographic (EEG) response (irregular line) to an intravenous infusion. Alfentanil shows a less time lag between the rise and fall of arterial concentration and the rise and fall of EEG response than fentanyl because it equilibrates with the brain more quickly. *Reprinted with permission from Scott JC, Ponganis KV, Stanski DR. EEG quantitation of narcotic effect: the comparative pharmacodynamics of fentanyl and alfentanil. Anesthesiology. 1985;62(3):234-241. Copyright © 1985 American Society of Anesthesiologists, Inc.*

The relationship between the plasma and the site of drug effect is modeled with an “effect site” model, as shown in [Figure 2.23](#).¹⁶ The site of drug effect is connected to the plasma by a first-order process. The equation that relates effect site concentration to plasma concentration is

$$\frac{dCe}{dt} = k_{e0} \cdot Cp - k_{e0} \cdot Ce$$

Equation 2.29

where Ce is the effect site concentration and Cp is the plasma drug concentration. k_{e0} is the rate constant for elimination of drug from the effect site. It is most easily understood in terms of its reciprocal, $0.693/k_{e0}$, the half-time for equilibration between the plasma and the site of drug effect.

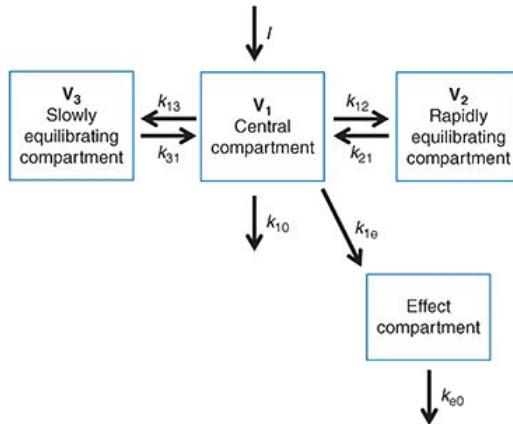


FIGURE 2.23 The three-compartment model from [Figure 2.16](#) with an added effect site to account for the equilibration delay between the plasma concentration and the observed drug effect. The effect site has a negligible volume. As a result, the only parameter that affects the delay is k_{e0} .

[Figure 2.24](#) shows the plasma and effect site concentrations predicted by the model (see [Figure 2.22](#)) for fentanyl and alfentanil. The plasma concentrations (*black lines*) are not very different. However, the effect site concentrations (*red lines*) show that alfentanil equilibrates more quickly. There are two consequences. First, the peak effect is sooner (obviously). Second, the rapid equilibration of alfentanil allows the brain to “see” the initial high plasma concentrations, producing a relatively greater rise in effect site concentrations than observed with fentanyl. This permits alfentanil to deliver relatively more “bang” for a bolus.

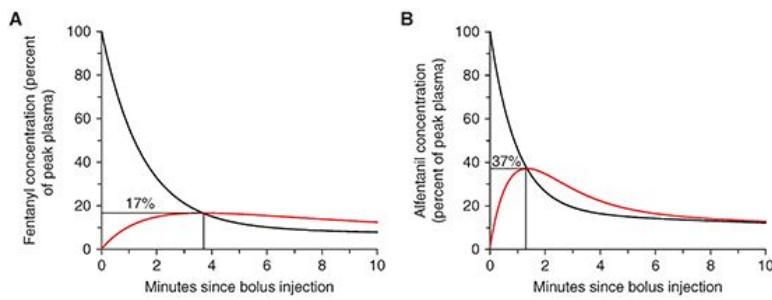


FIGURE 2.24 Plasma (black line) and effect site (red line) concentrations following a bolus dose of fentanyl (A) or alfentanil (B). Adapted with permission from Shafer SL, Varvel JR. Pharmacokinetics, pharmacodynamics, and rational opioid selection. *Anesthesiology*. 1991;74(1):53-63. Copyright © 1991 American Society of Anesthesiologists, Inc.

The constant k_{e0} has a large influence on the rate of rise of drug effect, the rate of offset of drug effect, the time to peak effect,¹⁷ and the dose that is required to produce the desired drug effect.

Dose Calculations

Bolus Dosing

We noted previously that we can rearrange the definition of concentration to find the amount of drug required to produce any desired target concentration for a known volume, amount = $C_T \times$ volume. Many introductory pharmacokinetic texts suggest using this formula to calculate the loading bolus required to achieve a given concentration. The problem with applying this concept to the anesthetic drugs is that there are several volumes: V_1 (central compartment); V_2 and V_3 (the peripheral compartments); and Vd_{ss} , the sum of the individual volumes. V_1 is usually much smaller than Vd_{ss} , and so it is tempting to say that the loading dose should be something between $C_T \times V_1$ and $C_T \times Vd_{ss}$.

That proves to be a useless suggestion. Consider the initial dose of fentanyl. The C_{50} for fentanyl to attenuate hemodynamic response to intubation (when combined with an intravenous hypnotic) is approximately 2 ng/mL. The V_1 and Vd_{ss} for fentanyl are 13 L and 360 L, respectively. The dose of fentanyl thus ranges from a low of 26 µg (based on the V_1 of 13 L) to a high 720 µg (based on the Vd_{ss} of 360 L). A fentanyl bolus of 26 µg achieves the desired concentration in the plasma for an initial instant (Figure 2.25). Unfortunately, the plasma levels almost instantly decrease below the desired target, and the effect site levels are never close to the desired target. A fentanyl bolus of 720 µg, not surprisingly, produces an enormous overshoot in the plasma levels that persists for hours. It is absurd to use equations to calculate the fentanyl dose if the resulting recommendation is “pick a dose between 26 and 720 µg.”

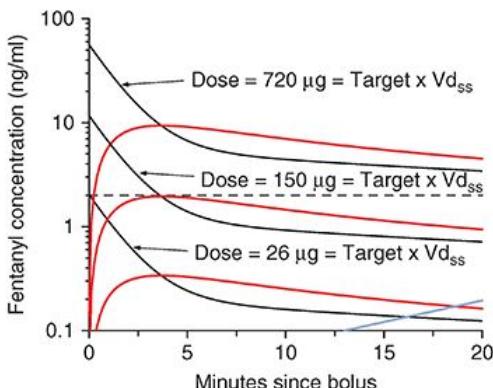


FIGURE 2.25 The volume of the central compartment of fentanyl is 13 L. The volume of distribution at steady state is 360 L. For a target concentration of 2 µg/L (dotted line), the dose calculated on V_1 , 26 µg, results in a substantial undershoot. The dose calculated using Vd_{ss} , 720 µg, produces a profound overshoot.

Only a dose based on $Vd_{peak\ effect}$, 150 µg, produces the desired concentration in the effect site. The black lines show plasma concentration over time. Red lines show effect site concentration over time.

Conventional approaches to calculate a bolus dose are designed to produce a specific *plasma* concentration. This makes little sense because the plasma is not the site of drug effect. By knowing the k_{e0} (the rate constant for elimination of drug from the effect site) of an intravenous anesthetic, we can design a dosing regimen that yields the desired concentration *at the site of drug effect*. If we do not want to overdose the patient, we should select the bolus that produces the desired peak concentration in the effect site.

The decline in plasma concentration after the bolus, up to the time of peak effect, can be thought of as a dilution of the bolus into a larger volume than the volume of the central compartment. One interesting characteristic of the equilibration between the plasma and the effect site is that at the time of peak effect, the plasma and the effect site concentrations are the same (if they were not the same, then it would not be the peak because there would be a gradient driving drug in or out of the effect site). This introduces the concept of Vd_{pe} , the apparent volume of distribution at the time of peak effect.¹⁸ The size of this volume can be readily calculated from the observation that the plasma and effect site concentrations are the same at the time of peak effect:

$$Vd_{pe} = \frac{\text{bolus amount}}{C_{pe}}$$

Equation 2.30

where C_{pe} is the plasma concentration at the time of peak effect. We can arrange this equation to calculate the dose that provides the desired peak effect site concentration: bolus dose = $C_T \times Vd_{pe}$. For example, the Vd_{pe} for fentanyl is 75 L. Producing a peak fentanyl effect site concentration of 2 ng/mL requires 150 µg for the typical patient, which produces a peak effect in 3.6 minutes. This is a much more reasonable dosing guideline than the previous recommendation of picking a dose between 26 and 760 µg. **Table 2.2** lists V_1 and Vd_{pe} for fentanyl, alfentanil, sufentanil, remifentanil, propofol, thiopental, and midazolam. **Table 2.3** lists the time to peak effect and the $t_{1/2} k_{e0}$ (half-life at the site of drug effect) of the commonly used intravenous anesthetics. Of course, individuals may differ from the typical patient. The individual characteristics that drive the differences may be known (age, weight, renal or hepatic dysfunction) in which case they can be built into the pharmacokinetic model if they are found to be significant. On the other hand, they may be unknown, in which case pharmacodynamic monitoring is required to fine tune dosing.

TABLE 2.2
Volume of distribution at the time of peak effect^a

Drug	V_1 (L)	Vd_{pe} (L)
Fentanyl	12.7	75
Alfentanil	2.19	5.9
Sufentanil	17.8	89
Remifentanil	5.0	17
Propofol	6.7	37
Thiopental	5.6	14.6
Midazolam	3.4	31

Abbreviations: V_1 , volume of the central compartment; Vd_{pe} , apparent volume of distribution at the time of peak effect.

^aReprinted from Glass PSA, Shafer SL, Reves JG. Intravenous drug delivery systems. In: Miller RD, Eriksson LI, Fleisher LA, et al, eds. *Miller's Anesthesia*. Vol 1. 7th ed. Philadelphia, PA: Churchill Livingstone; 2010:825-858. Copyright © 2010 Elsevier. With permission.

TABLE 2.3The time to peak effect and $t_{1/2} k_{e0}$ following a bolus dose^a

Drug	Time to peak drug effect (min)	$T_{1/2} k_{e0}$ (min) ^b
Fentanyl	3.6	4.7
Alfentanil	1.4	0.9
Sufentanil	5.6	3.0
Remifentanil	1.6	1.3
Propofol	2.2	2.4
Thiopental	1.6	1.5
Midazolam	2.8	4.0
Etomidate	2.0	1.5

^aReprinted from Glass PSA, Shafer SL, Reves JG. Intravenous drug delivery systems. In: Miller RD, Eriksson LI, Fleisher LA, et al, eds. *Miller's Anesthesia*. Vol 1. 7th ed. Philadelphia, PA: Churchill Livingstone; 2010:825-858. Copyright © 2010 Elsevier. With permission.

^b $t_{1/2} k_{e0} = 0.693/k_{e0}$, the effect site half-life, where k_{e0} is the rate constant for elimination of drug from the site of drug effect and $t_{1/2} k_{e0}$ is the time required for the concentration at the site of drug effect to fall to half of its value.

Maintenance Infusion Rate

As explained previously, to maintain a given target concentration, C_T , drug must be delivered at the same rate that drug is exiting the body. Thus, the maintenance infusion rate at steady state is maintenance infusion rate = $C_T \times Cl$. However, this equation only applies after peripheral tissues have fully equilibrated with the plasma, which may require many hours. At all other times, this maintenance infusion rate underestimates the infusion rate to maintain a target concentration.

In some situations, this simple rate calculation may be acceptable. For example, if an infusion at this rate is used after a bolus based on Vd_{pe} (apparent volume of distribution at time of peak effect), and the drug has a long delay between the bolus and peak effect, then much of the distribution of drug into the tissues may have occurred by the time of peak effect site concentration. In this case, the maintenance infusion rate calculated as clearance times target concentration may be satisfactory because Vd_{pe} is sufficiently higher than V_1 to account for the distribution of drug into peripheral tissues. Unfortunately, most drugs used in anesthesia have sufficiently rapid plasma-effect site equilibration that Vd_{pe} does not adequately encompass the distribution process, making this approach unsuitable.

The pharmacokinetically sound approach should account for tissue distribution. Initially, the infusion rate is higher than $C_T \cdot Cl$ because it is necessary to replace the drug that gets taken up by peripheral tissues. However, the net flow of drug into peripheral tissues decreases over time. Therefore, the infusion rate required to maintain any desired concentration must also decrease over time. Following bolus injection, the equation to maintain the desired concentration is:

$$\text{Maintenance infusion rate} = C_T \times V_1 \times (k_{10} + k_{12}e^{-k_{21}t} + k_{13}e^{-k_{31}t})$$

Equation 2.31

This equation indicates that a high infusion rate is initially required to maintain C_T . Over time, the infusion rate gradually decreases ([Figure 2.26](#)). At equilibrium ($t = \infty$), the infusion rate decreases to $C_T V_1 k_{10}$, which is the same as $C_T \times Cl$.

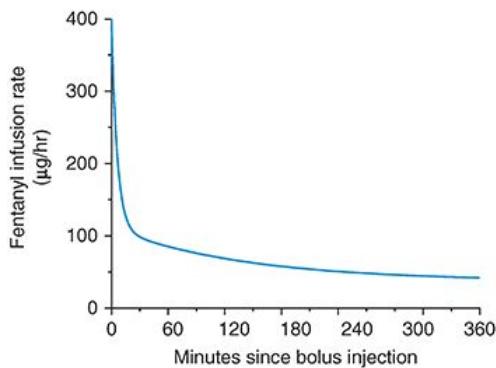


FIGURE 2.26 Fentanyl infusion rate to maintain a plasma concentration of 1 μg per hour. The rate starts off quite high because fentanyl is avidly taken up by body fat. The necessary infusion rate decreases as the fat equilibrates with the plasma.

No anesthetic in history has ever been so boring as to merit mentally solving such an equation while administration of an anesthetic. Fortunately, there are simple techniques that can be used in place of solving such a complex expression.

[Figure 2.27](#) is a nomogram in which the [Equation 2.14](#) has been solved, showing the infusion rates over time necessary to maintain any desired concentration of fentanyl, alfentanil, sufentanil, and propofol. This nomogram is complex, and we don't use it even though one of us (SLS) created this nomogram. The point in including it is to show how infusion rates must be turned down over time as drug accumulates. The y -axis represents the target concentration, C_T . The suggested target initial concentrations (shown in red) are based on the work of Vuyk and colleagues¹⁹ and appropriately scaled for fentanyl and sufentanil. The x -axis is the time since the beginning of the anesthetic. The intersections of the target concentration line and the diagonal lines indicates the infusion rate appropriate at each point in time. For example, to maintain a fentanyl concentration of 1.0 ng/mL, the appropriate rates are 3.0 $\mu\text{g}/\text{kg}/\text{hour}$ at 15 minutes, 2.4 $\mu\text{g}/\text{kg}/\text{hour}$ at 30 minutes, 1.8 $\mu\text{g}/\text{kg}/\text{hour}$ at 60 minutes, 2.1 $\mu\text{g}/\text{kg}/\text{hour}$ at 120 minutes, and 0.9 $\mu\text{g}/\text{kg}/\text{hour}$ at 180 minutes.

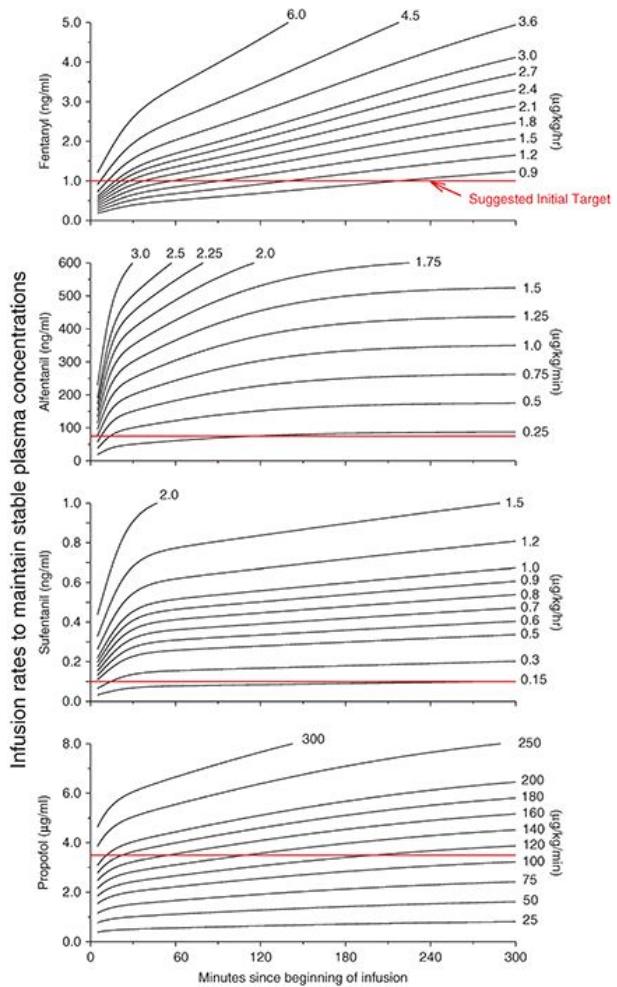


FIGURE 2.27 Dosing nomogram, showing the infusion rates (numbers on the perimeter) required to maintain stable concentrations of fentanyl (1.0 $\mu\text{g}/\text{mL}$), alfentanil (75 $\mu\text{g}/\text{mL}$), sufentanil (0.1 $\mu\text{g}/\text{mL}$), and propofol (3.5 ng/mL).

Another approach to determine infusion rates for maintenance of anesthesia to a desired target concentration is through the use of a specialized slide rule.²⁰ Figure 2.28 illustrates such a slide rule for propofol. As described by Bruhn et al,²⁰ “The bolus dose required to reach a given target plasma concentration is the product of the (weight-related) distribution volume and required concentration. Similarly, the infusion rate at a particular time point is the product of target concentration, body weight, and a correction factor that depends on the time elapsed from the start of the initial infusion. This factor can be determined for each time point using a PK simulation program.”

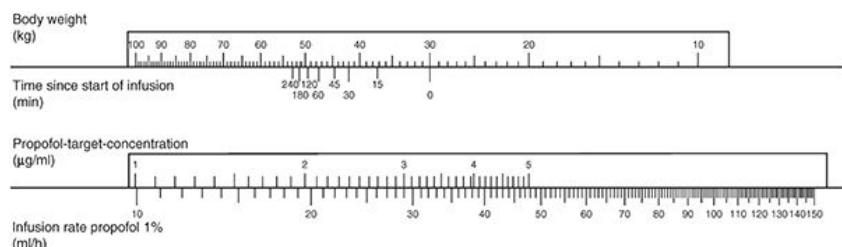


FIGURE 2.28 Propofol slide ruler to calculate maintenance infusion rate, based on the patient’s weight and the time since the start of the infusion, as proposed by Bruhn and colleagues. To make use of the calculator, make a photocopy and cut in to top (body weight), middle (time since start of infusion/propofol target

concentration), and bottom (infusion rate propofol 1%) sections—calculation requires sliding the middle piece in relationship to the top and bottom segments, which are fixed. *Adapted with permission from Bruhn J, Bouillon TW, Röpcke H, et al. A manual slide rule for target-controlled infusion of propofol: development and evaluation. Anesth Analg. 2003;96(1):142-147. Copyright © 2003 International Anesthesia Research Society.*

The best approach is through the use of target-controlled drug delivery. With target-controlled drug delivery, the user simply sets the desired plasma or effect site concentration. Based on the drug's pharmacokinetics and the mathematical relationship between patient covariates (eg, weight, age, gender) and individual pharmacokinetic parameters, the computer calculates the dose of drug necessary to rapidly achieve and then maintain any desired concentration. Most critically, it can raise and lower concentrations in a controlled fashion, a calculation that cannot be captured in any simple nomogram. Such computerized controlled drug delivery systems are now widely available.

An alternative approach is to use stanpumpR, which can be found online at <http://stanpumpR.io>. stanpumpR is an online, open-source (see <https://github.com/StevenLShaffer/stanpumpR>) pharmacokinetic simulator for intravenous anesthetic drugs and oral opioids. It was primarily developed by one of the authors (SLS) and remains in active development. **Figure 2.29** shows the screen of stanpumpR simulating an anesthetic with a propofol bolus and infusion, a fentanyl bolus, a remifentanil infusion, and two boluses of rocuronium. stanpumpR can be used to model specific anesthetic strategies before anesthesia or to model an ongoing anesthetic to see approximately what the drug levels are for the administered drugs.

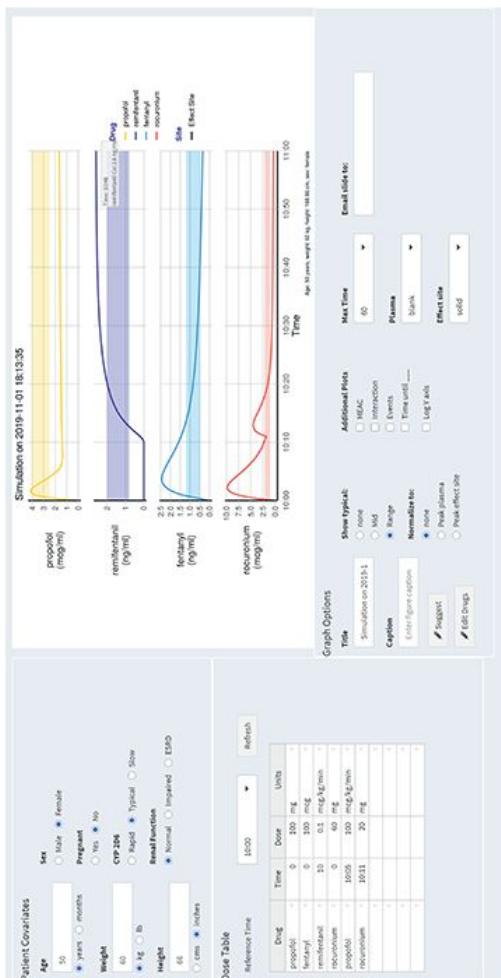


FIGURE 2.29 stanpumpR (<https://stanpumpR.io>) is a pharmacokinetic (PK)/pharmacodynamic (PD) simulation program for anesthesia. The program implements published PK/PD models for alfentanil, dexmedetomidine, etomidate, fentanyl, hydromorphone, ketamine, lidocaine, methadone, midazolam, morphine, naloxone, oxycodone, oxytocin, pethidine, propofol, remifentanil, rocuronium, and sufentanil.

Context-Sensitive Half-time

Special significance is often ascribed to the smallest exponent, which determines the slope of the final log-linear portion of the curve. When the medical literature refers to the half-life of a drug, unless otherwise stated, the half-life is based on the terminal half-life (ie, $0.693/\text{smallest exponent}$). However, the terminal half-life for drugs with more than one exponential term is nearly impossible to interpret. The terminal half-life sets an upper limit on the time required for the concentrations to decrease by 50% after drug administration. Usually, the time for a 50% decrease will be much faster than that upper limit. A more useful concept is the “context-sensitive half-time,” shown in [Figure 2.30](#),²¹ which is the time for the plasma concentration to decrease by 50% from an infusion that maintains a constant concentration. The “context” is the duration of the infusion. The context-sensitive half-time increases with longer infusion durations because it takes longer for the concentrations to fall if drug has accumulated in peripheral tissues.

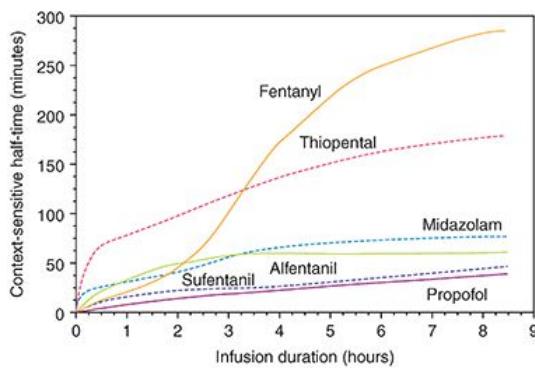


FIGURE 2.30 Context-sensitive half-times as a function of the duration of intravenous drug infusion for alfentanil, sufentanil, propofol, midazolam, and thiopental. Reprinted with permission from Hughes MA, Glass PSA, Jacobs JR. Context-sensitive half-time in multicompartment pharmacokinetic models for intravenous anesthetic drugs. *Anesthesiology*. 1992;76(3):334-341. Copyright © 1992 American Society of Anesthesiologists, Inc.

The context-sensitive half-time is based on the time for a 50% decrease, which was chosen both to provide an analogy to half-life, and because, very roughly, a 50% reduction in drug concentration appears necessary for recovery after administration of most intravenous hypnotics at the termination of surgery. Of course, decreases other than 50% may be clinically relevant. Additionally, the context-sensitive half-time does not consider plasma-effect site disequilibrium and thus may be misleading for drugs with very slow plasma-effect site equilibration. A related but more clinically relevant representation is the context-sensitive effect site decrement time, as shown in [Figure 2.31](#).²² For example, the upper black line in [Figure 2.31](#) is the context-sensitive 20% effect site decrement time for fentanyl, that is, the time required for fentanyl effect site concentrations to fall by 20%, based on the duration of a fentanyl infusion. Context-sensitive half-time and effect site decrement times are more useful than elimination half-time in characterizing the clinical responses to drugs.²³

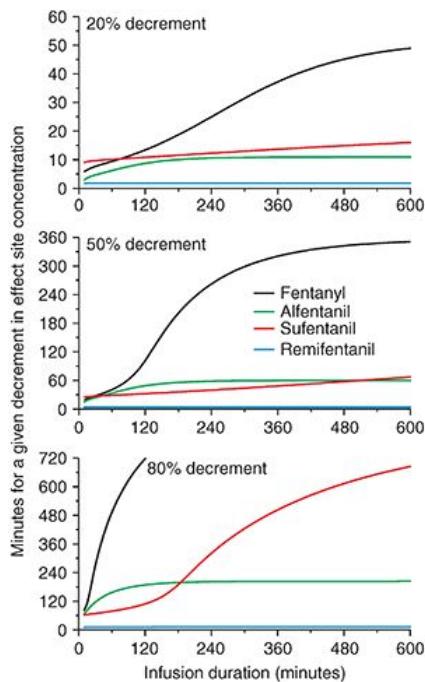


FIGURE 2.31 Effect site decrement times. The 20%, 50%, and 80% decrement times for fentanyl (black), alfentanil (green), sufentanil (red), and remifentanil (blue). When there is substantial plasma-effect site disequilibrium, the effect site decrement time will provide a better estimate of the time required for recovery than the context-sensitive half-time. *Adapted from Youngs EJ, Shafer SL. Pharmacokinetic parameters relevant to recovery from opioids. Anesthesiology. 1994;81:833-842.*

Pharmacodynamics

Pharmacodynamics is the study of the intrinsic sensitivity or responsiveness of the body to a drug and the mechanisms by which these effects occur. Thus, pharmacodynamics may be viewed as what the drug does to the body. Structure-activity relationships link the actions of drugs to their chemical structure and facilitate the design of drugs with more desirable pharmacologic properties. The intrinsic sensitivity is determined by measuring plasma concentrations of a drug required to evoke specific pharmacologic responses. The intrinsic sensitivity to drugs varies among patients and within patients over time with changes in physiology such as aging, disease, and injury. As a result, at similar plasma concentrations of a drug, some patients show a therapeutic response, others show no response, and others develop toxicity.

The basic principles of receptor theory were covered in the first section of this chapter. This section focuses on methods of evaluating clinical drug effects such as dose-response curves, efficacy, potency, the median effective dose (ED_{50}), the median lethal dose (LD_{50}), and the therapeutic index.

Concentration Versus Response Relationships

The most fundamental relationship in pharmacology is the concentration (or dose) versus response curve, shown in [Figure 2.32](#). This is the time-independent relationship between exposure to the drug (x-axis) and the measured effect (y-axis). The exposure can be the concentration, the dose, the area under the concentration versus time curve, or any other measure of drug exposure that is clinically meaningful. The measured effect can be an absolute response (eg, twitch height), a normalized response (eg, percentage of twitch depression), a population response (eg, fraction of subjects moving at incision), or any physiologic response (chloride current). The standard equation for this relationship is the “Hill” equation, sometimes called the **sigmoid-E_{max} relationship**:

$$\text{Effect} = E_0 + (E_{\max} - E_0) \frac{C^{\gamma}}{C_{50}^{\gamma} + C^{\gamma}}$$

Equation 2.32

In this equation, E_0 is the baseline effect in the absence of drug, and E_{\max} is the maximum possible drug effect. C is typically concentration or dose, although other measures of drug exposure (eg, dose, peak concentration, area under the concentration vs time curve) can be used. C_{50} is the concentration associated

with 50% of peak drug effect and is a measure of drug potency. The term $\frac{C^{\gamma}}{C_{50}^{\gamma} + C^{\gamma}}$ is a modification of the saturation equation $\frac{C}{C_{50} + C}$ presented in the prior section. Previously, it did not have an exponent. However, when used in pharmacodynamic models, the exponent γ , also called the **Hill coefficient**, appears. The exponent relates to the “sigmoidicity” and steepness of the curve. If γ is less than 1 and the curve is plotted on a standard x -axis, then the curve appears hyperbolic (see [Figure 2.8](#)). If γ is greater than 1, then the curve appears sigmoidal, as in [Figure 2.32](#). If the x -axis is plotted on a log scale, then the curve will always appear sigmoidal regardless of the value of γ .

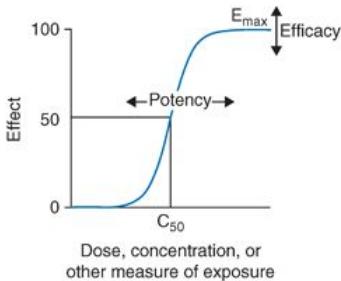


FIGURE 2.32 Drug exposure (dose, concentration, etc) versus drug effect relationship. Potency refers to the position of the curve along the x -axis. Efficacy refers to the position of the maximum effect on the y -axis.

Potency and Efficacy

There are two problems with the term **potency**. Clinicians often use potency to refer to the relative dose of two drugs, such as the relative potency of fentanyl and morphine. The problem with this definition is that when drugs have very different time courses, the relative potency varies depending on the time of the measurement. Fentanyl reaches peak effect 3.5 minutes after injection. Morphine reaches peak effect 90 minutes after injection. As a result, the “relative potency” 3.5 minutes after injection indicates that fentanyl is far more potent than morphine. However, when morphine has reached its peak effect 90 minutes after injection, the effect of the fentanyl has almost entirely dissipated. Measured 90 minutes after injection, morphine is more potent. From therapeutic perspective, potency is often defined in terms of relative doses without regard to time. This common practice, unfortunately, is scientifically flawed.

From a pharmacologic perspective, potency is described based on the concentration versus response relationship. As shown in [Figure 2.33](#), a drug with a left-shifted concentration versus response curve (ie, lower C_{50}) is considered more potent, whereas a drug with a right-shifted dose versus response curve is less potent. To be precise, potency should be defined in terms of a specific drug effect (eg, 50% of maximal effect of a full agonist). This is particularly important if the two drugs have differing Hill coefficients or efficacies (E_{\max}).

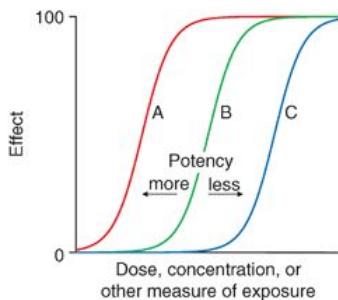


FIGURE 2.33 Dose versus response relationship for three drugs with potency. Drug A is the most potent, and drug C is the least potent.

Efficacy is a measure of the intrinsic ability of a drug to produce a given physiologic or clinical effect (see [Figure 2.32](#)). Consider the example of benzodiazepines given earlier (see [Figure 2.3](#)). Intrinsic efficacy ranged from full effect for midazolam to partial effect for bretazenil to no effect for flumazenil. The difference between a full agonist, a partial agonist, and an antagonist represents differences in efficacy. Efficacy refers to the position of the concentration versus response curve in the y-axis, whereas potency refers to relative drug concentration for a particular response on the y-axis.

Two drugs may have the same C_{50} but different efficacies. Because C_{50} is defined relative to the maximum drug effect, the drug with lower efficacy demonstrates less effect at C_{50} ([Figure 2.34](#)) and is therefore less potent. This introduces the second problem with the term potency. One can only compare potencies by comparing C_{50} values if the maximum effect and the Hill coefficient are identical for both drugs. If not, then potency must be described in terms of a specific drug effect (a specific point on the y-axis of the dose vs response curve).

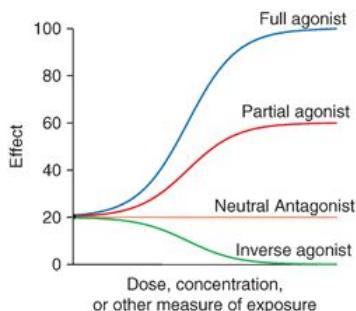


FIGURE 2.34 Concentration versus response curves for drugs with differing efficacies. Although the C_{50} of each curve is the same, the partial agonist is less potent than the full agonist because of the decreased efficacy.

Effective Dose and Lethal Dose

The ED_{50} is the dose of a drug required to produce a specific desired effect in 50% of individuals receiving the drug. The LD_{50} is the dose of a drug required to produce death in 50% of patients (or, more often, animals) receiving the drug. The therapeutic index is the ratio between the LD_{50} and the ED_{50} (LD_{50}/ED_{50}). The larger the therapeutic index of a drug, the safer the drug is for clinical administration. The relationship among ED_{50} , LD_{50} , and therapeutic index is shown in [Figure 2.33](#). The classic calculation of LD_{50} is not clinically very helpful in anesthesia where we expect 100% of patients to fall asleep and nobody to die. However, anesthetics have very narrow therapeutic windows. A more effective ratio is the LD_1/ED_{99} ratio. That ratio shows a far smaller margin of safety and actually is reversed in [Figure 2.35](#), meaning that there is appreciable risk of death, even at subtherapeutic doses in some individuals. Anesthetic drugs have uniquely

low therapeutic ratio. For example, the LD₅₀ for sevoflurane has been estimated to be 2.6.²⁴ This is why enormous vigilance is necessary for safe use of inhaled anesthetics.

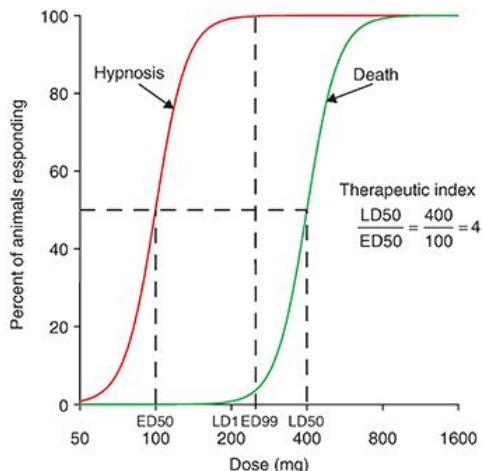


FIGURE 2.35 Analysis to determine the median lethal dose in 50% of the animals (LD₅₀), the median lethal dose in 99% of the animals (LD₉₉), and the therapeutic index of a drug.

Drug Interactions

Actions at Different Receptors

Opioids potently reduce the minimum alveolar concentration (MAC) of inhaled anesthetics required to suppress movement to noxious stimulation (Figure 2.36).^{25,26} Initially, the interaction is profound, with approximately 50% reduction in MAC at a plasma fentanyl concentration of 1.5 ng/mL. However, after the initial reduction in MAC, there is fairly limited benefit from additional fentanyl. The clinical pearl is that a modest amount of opioid dramatically reduces the concentrations of inhalational anesthetic required to prevent movement. The second pearl is that even with huge doses of opioids, some hypnotic component must be added to the anesthetic to prevent movement.

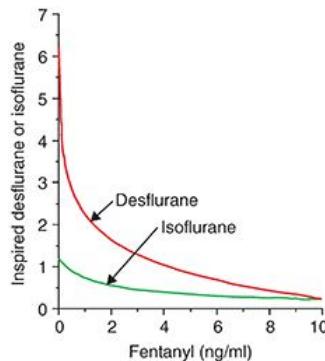


FIGURE 2.36 Interaction between fentanyl and isoflurane or desflurane on the minimum alveolar concentration required to suppress movement to noxious stimulation. Adapted from Sebel PS, Glass PS, Fletcher JE, Murphy MR, Gallagher C, Quill T. Reduction of the MAC of desflurane with fentanyl. Anesthesiology. 1992;76:52-59; McEwan AI, Smith C, Dyar O, Goodman D, Smith LR, Glass PS. Isoflurane minimum alveolar concentration reduction by fentanyl. Anesthesiology. 1993;78:864-869.

Similar work has been done for propofol. Vuyk and colleagues¹⁹ characterized the interaction of propofol with alfentanil. As shown in Figure 2.37, the interaction is markedly synergistic, with modest amounts of alfentanil greatly decreasing the amount of propofol associated with 50% chance of response to

intubation or surgical incision. Vuyk and colleagues¹⁹ also documented a similar interaction of propofol and alfentanil on return of consciousness.

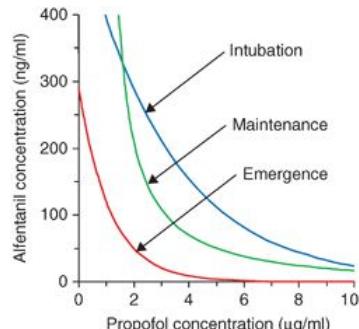


FIGURE 2.37 Interaction of propofol with alfentanil on the concentration required to suppress response to intubation, maintain nonresponsiveness during surgery and then awaken from anesthesia. Adapted with permission from Vuyk J, Lim T, Engbers FH, et al. The pharmacodynamics interaction of propofol and alfentanil during lower abdominal surgery in women. *Anesthesiology*. 1995;83(1):8-22. Copyright © 1995 American Society of Anesthesiologists, Inc.

Hendrickx and colleagues²⁷ surveyed the interaction of anesthetic drugs that affect nociception, analgesia, and hypnosis (Figure 2.38). They examined two endpoints: “hypnosis,” defined as loss of consciousness in humans and loss of righting reflex in animals, and “immobility,” defined as the loss of movement response to noxious stimulation in a nonparalyzed subject. As shown in Figure 2.38, the interaction between pairs of intravenous drugs and intravenous drugs and inhaled anesthetics is typically synergistic. An exception is the combination of the NMDA antagonists, ketamine and nitrous oxide, which demonstrate synergy, additivity, or infra-additivity in different models that have been studied. By contrast, the inhaled anesthetics are strictly additive in their interactions with other inhaled anesthetics, potentially suggesting a common mechanism of action.

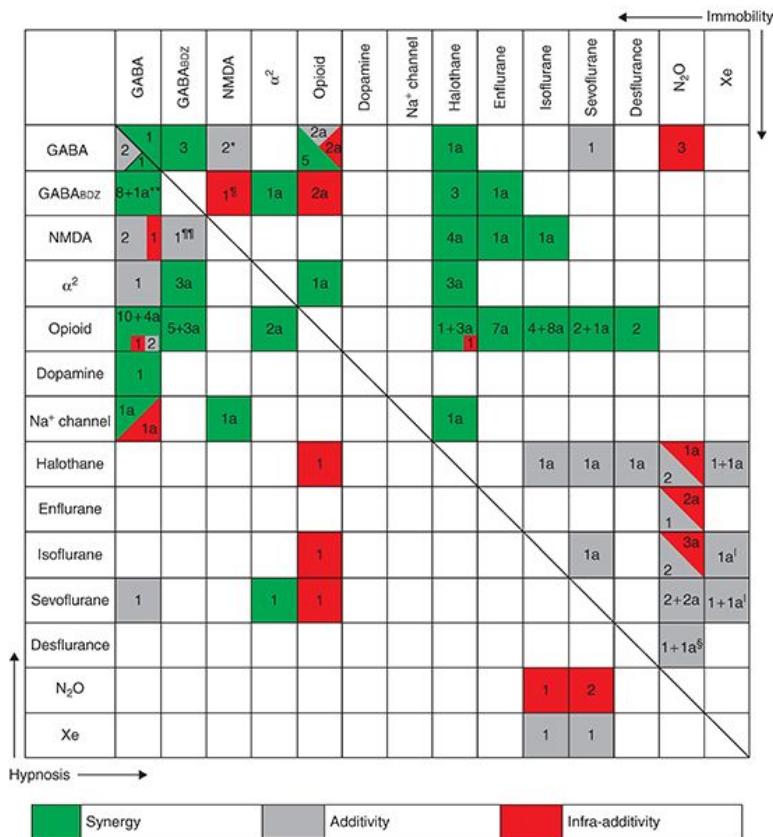


FIGURE 2.38 Survey of interactions between hypnotics and analgesics by Hendrickx et al. Reprinted with permission from Hendrickx JF, Eger EI II, Sonner JM, et al. Is synergy the rule? A review of anesthetic interactions producing hypnosis and immobility. Anesth Analg. 2008;107(2):494-550. Copyright © 2008 International Anesthesia Research Society.

Classic interaction studies, such as those described earlier, examine the concentrations associated with a particular response (such as a 50% chance of moving) for two drugs, evaluated separately and in combination. However, a more general view is that any combination of two drugs is associated with a response. This is best viewed as a “response surface” in which the x-axis and y-axis of the surface are concentrations (or doses) of drugs A and B, and the Z axis is the response to the particular combination. Minto et al²⁸ proposed a mathematical framework for response surfaces for a variety of interaction surfaces of interest to anesthesiologists. [Figure 2.39](#) shows six examples of possible response surfaces, depending on the nature of the interaction.

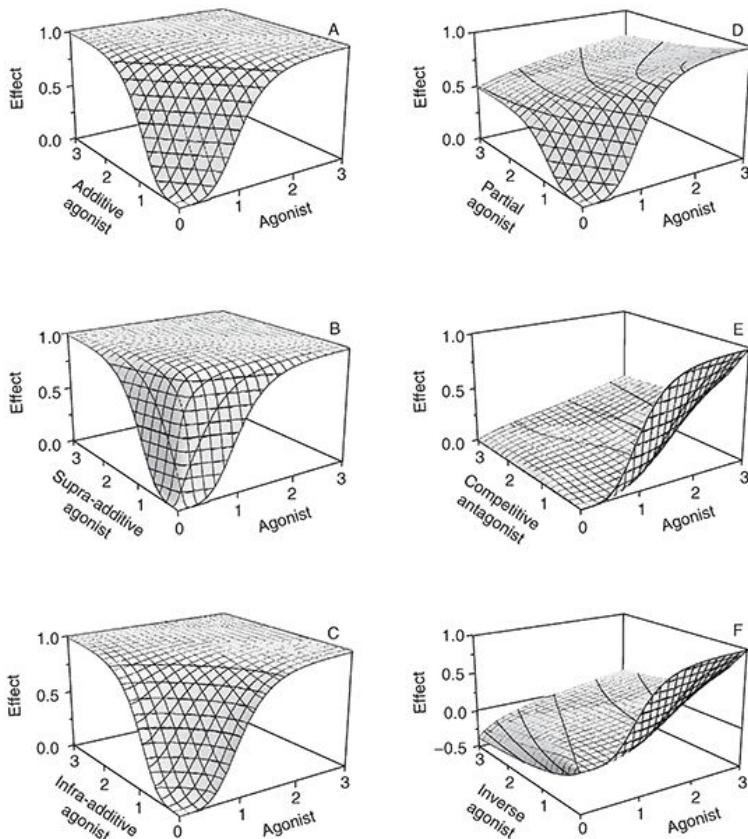


FIGURE 2.39 Interaction surfaces, showing simple additivity (A), synergy (B), and infra-additivity (C). More complex relationships exist between agonists and partial agonists (D), agonists and competitive antagonists (E), and agonists and inverse agonists (F). Reprinted with permission from Minto CF, Schnider TW, Short TG, et al. Response surface model for anesthetic drug interactions. Anesthesiology. 2000;92(6):1603-1616. Copyright © 2000 American Society of Anesthesiologists, Inc.

Stereochemistry

Stereochemistry is the study of how molecules are structured in three dimensions.^{29,30} **Chirality** is a unique subset of stereochemistry, and the term **chiral** is used to designate a molecule that has a center (or centers) of three-dimensional asymmetry. This kind of molecular configuration is almost always a function of the unique, tetrahedral bonding characteristics of the carbon atom.

Chirality is the structural basis of **enantiomerism**. Enantiomers are a pair of molecules existing in two forms that are mirror images of one another (right-handed and left-handed) but cannot be superimposed. In every other aspect, enantiomers are chemically identical. A pair of enantiomers is distinguished by the direction in which they rotate polarized light in solution. If the rotation is clockwise, then it is the D (dextrorotatory) or “+” enantiomer. If it is counterclockwise, then it is the L (levorotatory) or “-” enantiomer. The characteristic of rotation of polarized light is the origin of the term **optical isomers**. When the two enantiomers are present in equal proportions (50:50), they are referred to as a **racemic mixture**. A racemic mixture does not rotate polarized light (actually, because it rotates light equally both clockwise and counterclockwise, these effects cancel each other out so that the light is not rotated).

R and S designations have nothing to do with rotating light but are assigned based on numbering the atoms around the chiral center. D and L are the preferred nomenclature for referring to enantiomers.

When the two enantiomers are present in equal proportions (50:50), they are referred to as a **racemic mixture**.

The labels D and L are often confused with the designations R (rectus) and S (sinister) used in protein and carbohydrate chemistry. These classifications have nothing to do with rotating polarized light but are determined based on a formula for numbering each atom around the chiral center and then determining if the order is clockwise or counterclockwise.³⁰

Nearly every organic building block in biology is chiral, as are the resulting proteins, sugars, and lipids are chiral. As a result, the interaction of enantiomers with plasma proteins, membrane transporters, receptors, and metabolic enzymes will depend on the specific stereochemistry of the molecule because these interactions are invariably three-dimensionally exacting.^{29,30} Enantiomers can exhibit differences in absorption, distribution, clearance, potency, and toxicity (drug interactions). Enantiomers can even antagonize the effects of one another.

The administration of a racemic drug mixture represents two different drugs with distinct pharmacokinetic and pharmacodynamic properties. Only one enantiomer may be therapeutically active, whereas the other contributes to side effects. The therapeutically inactive isomer in a racemic mixture should be regarded as an impurity.³¹ An estimated one-third of drugs in clinical use are administered as racemic mixtures. Their use is likely to decrease in the future although the clinical advantages of single enantiomers must be balanced against the increased costs of drugs.³⁰ Regulatory agencies and pharmaceutical companies are aware of the importance of identification of the therapeutic enantiomer and strive to avoid approving new racemic mixtures.³²

Clinical Aspects of Chirality

More than one-third of all synthetic drugs are chiral, although most of them are utilized clinically as racemic mixtures.^{30,33} The majority of inhaled anesthetics are chiral with the notable exception of sevoflurane. Most evidence suggests that enantiomer-selective effects for volatile anesthetics are relatively weak in contrast to much stronger evidence for specific drug-receptor interactions for intravenous anesthetics.³³ Local anesthetics, including mepivacaine, prilocaine, and bupivacaine, have a center of molecular asymmetry. The S (+) enantiomer of ketamine is more potent than the R (-) form and is also less likely to produce emergence delirium. Similarly, in addition to pharmacokinetic differences, the cardiac toxicity of bupivacaine is thought to be predominantly due to the R-bupivacaine isomer. Ropivacaine is the S-enantiomer of a bupivacaine homolog, which has decreased cardiac toxicity. Likewise, the S-enantiomer of bupivacaine, levobupivacaine, is associated with less cardiac toxicity than bupivacaine. Cisatracurium is an isomer of atracurium that lacks histamine-releasing potential. Methadone is a racemic mixture of an opioid (L methadone) and a potent NMDA antagonist (D methadone). Based on demonstration of S-ketamine as an effective treatment for refractory depression, several companies are investigating d-methadone as a possible antidepressant without the psychotomimetic effects of ketamine.³⁴ Anesthetic drugs derived from natural precursors, such as curare (*d*-tubocurarine) and morphine (*l*-morphine), are not racemic because natural synthesis is invariably stereospecific.²⁹

Individual Variability

The response to drugs varies greatly among patients.³⁵ After administration of identical doses, some patients may have clinically significant adverse effects, whereas others may exhibit no therapeutic response. Some of this diversity of response can be ascribed to differences in the rate of drug metabolism, particularly by the CYP family of enzymes. The incorporation of pharmacogenetics into clinical medicine may become useful in predicting patient responses to drugs.

Variability of individual responses to a drug often reflects differences in pharmacokinetics and/or pharmacodynamics among patients (**Table 2.4**).⁴ This may even account for differences in pharmacologic effects of drugs in the same patient at different times. Accurate dosing is difficult to achieve in the presence of interindividual variability and it is not unusual to find a twofold or more variation in plasma concentrations achieved in different individuals using the same dosing scheme. This is true for inhaled as well as injected drugs. Furthermore, there may be a fivefold range in the plasma concentrations of a drug required to achieve

the same pharmacologic effect in different individuals, and this range may be even greater if tolerance has developed in some individuals.

TABLE 2.4

Events responsible for variations in drug responses between individuals

Pharmacokinetics
Bioavailability
Renal function
Hepatic function
Cardiac function
Patient age
Pharmacodynamics
Enzyme activity
Genetic differences
Drug interactions

The relative importance of the numerous factors that contribute to variations in individual responses to drugs depends, in part, on the drug itself and its usual route of excretion. Drugs excreted primarily unchanged by the kidneys tend to exhibit smaller differences in pharmacokinetics than drugs that are metabolized by the liver.

As discussed previously, changes in metabolic rate have little impact on drugs with a high extraction ratio as the efficiency of extraction is so great that hepatic blood flow is a more rate-limiting factor than metabolism. Conversely, the systemic clearance of low-extraction drugs is highly susceptible to small changes in the rate of metabolism. For example, the systemic clearance of alfentanil is exquisitely sensitive to CYP induction and inhibition, whereas clearance of high-extraction opioids such as fentanyl and sufentanil is minimally influenced.³⁶ Remifentanil is the extreme example: The only significant covariate of remifentanil metabolism is age.

Interindividual variability in the metabolism of codeine, a prodrug, to morphine, the active metabolite, is determined by activity of CYP2D6-mediated *O*-demethylation to morphine and morphine-6-glucuronide. CYP2D6-deficient individuals have diminished or absent morphine formation following administration of codeine, whereas individuals with CYP2D6 gene amplification experience exaggerated opioid effects following administration of codeine (“codeine intoxication”).³⁷ Quinidine inhibits CYP2D6 and markedly diminishes codeine metabolism the active metabolite, morphine.

The dynamic state of receptor concentrations, as influenced by diseases and other drugs, also influences the variation in drug responses observed among patients. Finally, inhaled anesthetics, by altering circulatory, hepatic, and renal function, may influence the pharmacokinetics of injected drugs.

In clinical practice, the impact of interpatient variability may be masked by the administration of high doses of a drug. For example, the administration of 2 to 3 × ED₉₅ of a nondepolarizing neuromuscular blocking drug is common practice for achieving a skeletal muscle paralysis in all patients. Interpatient variability, however, is manifest if the level of neuromuscular blockade and duration of action is monitored. Furthermore, it is common practice in anesthesia to administer drugs in proportion to body weight, although pharmacokinetic and pharmacodynamic principles may not support this practice. In attempts to minimize interindividual variability, computerized infusion systems (target-controlled infusion systems) have been developed to deliver intravenous drugs (alfentanil, remifentanil, etomidate, propofol) to achieve a desired (target) concentration (reviewed in Glass et al³). Programs such as stanpumpR (<https://stanpumpR.io>) incorporate variability into the pharmacokinetic simulations provided that influence of the variability has been quantified mathematically.

Elderly Patients

In elderly patients, variations in drug response most likely reflect (1) decreased cardiac output, (2) increased fat content, (3) decreased protein binding, and (4) decreased renal function. Decreased cardiac output

decreases hepatic blood flow and, thus, delivery of drug to the liver for metabolism. This decreased delivery, combined with the possibility of decreased hepatic enzyme activity, may prolong the duration of action of drugs such as lidocaine and fentanyl.³⁸ An enlarged fat compartment may increase the *Vd* and lead to the accumulation of lipid-soluble drugs such as diazepam and thiopental.³⁹ Increased total body fat content and decreased plasma protein binding of drugs accounts for the increased *Vd* that accompanies aging. A parallel decrease in total body water accompanies increased fat stores. The net effect of these changes is an increased vulnerability of elderly patients to cumulative drug effects. Effects of age on pharmacokinetics and pharmacodynamics are discussed in detail in [Chapter 46](#).

Enzyme Activity

Alterations in enzyme activity as reflected by enzyme induction may be responsible for variations in drug responses among individuals. For example, cigarette smoke contains polycyclic hydrocarbons that induce mixed-function hepatic oxidases, leading to increased dose requirements for drugs such as theophylline and tricyclic antidepressants. Acute alcohol ingestion can inhibit metabolism of drugs. Conversely, chronic alcohol use (>200 g per day) induces microsomal enzymes that metabolize drugs. Because of enzyme induction, this accelerated metabolism may manifest as tolerance to drugs such as barbiturates.

Genetic Disorders

Variations in drug responses among individuals are due, in part, to genetic differences that may also affect receptor sensitivity. Genetic variations in metabolic pathways (rapid vs slow acetylators) may have important clinical implications for drugs such as isoniazid and hydralazine. **Pharmacogenetics** describes genetically determined disease states that are initially revealed by altered responses to specific drugs. Examples of diseases that are unmasked by drugs include (1) atypical cholinesterase enzyme revealed by prolonged neuromuscular blockade after administration of succinylcholine or mivacurium; (2) malignant hyperthermia triggered by succinylcholine or volatile anesthetics; (3) glucose-6-phosphate dehydrogenase deficiency, in which certain drugs cause hemolysis; and (4) intermittent porphyria, in which barbiturates may evoke an acute attack.

Drug Interactions

A drug interaction occurs when a drug alters the intensity of pharmacologic effects of another drug given concurrently. Drug interactions may reflect alterations in pharmacokinetics (increased metabolism of neuromuscular blocking drugs in patients receiving anticonvulsants chronically) or pharmacodynamics (decrease in volatile anesthetic requirements produced by opioids). The net result of a drug interaction may be enhanced or diminished effects of one or both drugs, leading to desired or undesired effects. A physicochemical drug interaction occurs when two incompatible drugs are mixed in the same solution (precipitate of the conjugate salt of a weak acid and weak base when vecuronium and thiopental are mixed together in the same intravenous tubing). The potential for drug interactions in the perioperative period is great, considering the large number of drugs from different chemical classes that are likely to be part of anesthesia management. For example, a typical “balanced anesthetic” may include benzodiazepines, sedative-hypnotics, opioids, neuromuscular blocking drugs, anticholinergics, anticholinesterases, sympathomimetics, sympathetic nervous system blocking drugs, and antibiotics.

An example of a beneficial drug interaction is the concurrent administration of propranolol with hydralazine to prevent compensatory increases in heart rate that would offset the blood pressure-lowering effects of hydralazine. Interactions between drugs are frequently used to counter the effects of agonist drugs, as reflected by the use of naloxone to antagonize opioids. Adverse drug interactions typically manifest as impaired therapeutic efficacy and/or enhanced toxicity. In this regard, one drug may interact with another to (1) impair absorption, (2) compete with the same plasma protein-binding sites, (3) alter metabolism by enzyme induction or inhibition, or (4) change the rate of renal excretion.

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PART II Neurologic System

Neurophysiology*

Updated by: Pamela Flood • Cassandra Bailey

The most amazing aspect of the daily miracle of anesthesia is turning off consciousness to permit surgery to proceed and then fully restoring consciousness in a controlled manner. We still do not know how this miracle occurs. A full understanding of consciousness, and the biology that underlies it, may be decades in the future, if it is tractable at all.¹ However, recent advances in neurophysiology are providing insight into how perioperative drugs interact with receptors throughout the nervous system to mediate anesthesia and analgesia. These concepts are likely familiar from previous training, but we review them to build our understanding of anesthetic and analgesic effects.

How Nerves Work

Neurons

Neurons are the basic element of all rapid signal processing within the body. A neuron consists of a cell body, also called the soma, dendrites, and the nerve fiber, also called the axon. Dendrites are highly specialized extensions of the cell body. The axon of one neuron commonly terminates (synapses) near the cell body or dendrites of another neuron. The axon connects to a neighboring cell with a *presynaptic terminal*. The *synaptic cleft* separates the presynaptic terminal and the cell body or dendrites of the next neuron in the signaling cascade. Transmission of impulses between neurons at a synapse is mediated by the release of a chemical mediator (neurotransmitter), such as *glutamate* or *γ-aminobutyric acid* (GABA) from the presynaptic terminal or in some cases direct activation through gap junctions. The membrane of the postsynaptic neurons contains receptors that bind neurotransmitters released from presynaptic nerve terminals, transducing the signal.

After signal transduction, the impulse travels along the nerve membrane as an *action potential*. This is entirely mediated by the channels within the membrane. Indeed, removal of the axoplasm from the nerve fiber does not alter conduction of impulses. Nerve fibers derive their nutrition from the cell body. Interruption of a nerve fiber causes the peripheral portion to degenerate (Wallerian degeneration). The axon of a peripheral neuron is able to regenerate, as does the myelin sheath. Regeneration has previously been thought to be the exception in most of the brain and spinal cord. Extensive research is underway to better understand the conditions that are required for central neuron regeneration to improve recovery from central neuronal injury.²

Classification of Afferent Nerve Fibers

Nerve fibers are called afferent if they transmit impulses from peripheral receptors to the central nervous system (CNS) and efferent if they transmit impulses from the CNS to the periphery. Afferent nerve fibers are classified as A, B, and C on the basis of fiber diameter and velocity of conduction of nerve impulses ([Table 3.1](#)). Conduction speed increases with nerve diameter because the larger diameter nerves have decreased longitudinal resistance to ion flux.³ The largest, and hence fastest, nerves are designated type A. Type A fibers are subdivided into alpha, beta, gamma, and delta. Type A- α_1 fibers innervate muscle spindles, and A- α_{1b} innervate the Golgi tendon organ. Both A- α afferents are important to muscle reflexes and control of muscle tone.

TABLE 3.1

Classification of peripheral nerve fibers

	Myelinated	Fiber diameter (μm)	Conduction velocity (m/s)	Function	Sensitivity to local anesthetic (subarachnoid, procaine, %)
A- α	Yes	12-20	70-120	Innervation of skeletal muscles Proprioception	1
A- β	Yes	5-12	30-70	Touch Pressure	1
A- γ	Yes	3-6	15-30	Skeletal muscle tone	1
A- δ	Yes	2-5	12-30	Fast pain Touch Temperature	0.5
B	Yes	3	3-15	Preganglionic autonomic fibers	0.25
C	No	0.4-1.2	0.5-2.0	Slow pain Touch Temperature Postganglionic sympathetic fibers	0.5

All cutaneous mechanoreceptors (Meissner corpuscles, hair receptors, Pacinian corpuscles) transmit signals in type A- β fibers. Touch and fast pain are transmitted by lightly myelinated type A- δ fibers with free nerve endings. Type C fibers transmit slow pain, pruritus, and temperature sensation.

Myelin that surrounds type A and B nerve fibers acts as an insulator that prevents flow of ions across nerve membranes. Type C fibers are unmyelinated. The myelin sheath is interrupted approximately every 1 to 2 μm by the nodes of Ranvier.⁴ Ions can flow freely between nerve fibers and extracellular fluid at the nodes of Ranvier. Action potentials are conducted from node to node by the myelinated nerve rather than continuously along the entire fiber as occurs in unmyelinated nerve fibers. This successive excitation of nodes of Ranvier by an action potential that jumps between successive nodes is termed *saltatory (or jumping) conduction* ([Figure 3.1](#)).⁴ Saltatory conduction allows for a 10-fold increase in the velocity of nerve transmission.³ It also conserves the membrane potential because only the membrane at the node of Ranvier depolarizes, resulting in less ion transfer than would otherwise occur. Furthermore, because depolarization is limited to the nodes of Ranvier, little energy is needed to reestablish the transmembrane sodium and potassium ion concentration gradients necessary for signal transmission. The energy savings is more than a hundredfold. As brilliantly understated by Hartline and Colman, “For a nervous system such as ours, which already accounts for 20% of the body’s resting metabolic energy budget, this is not an inconsequential advantage.”³

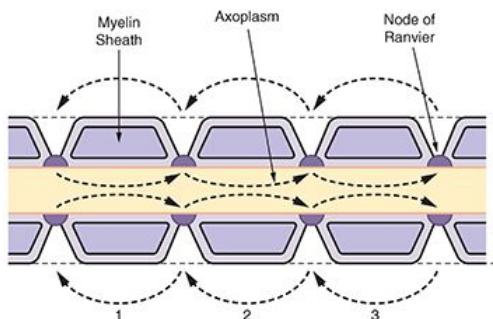


FIGURE 3.1 Saltatory conduction is transmission of nerve impulses that jump between successive nodes of Ranvier of myelinated nerves.

Evaluation of Peripheral Nerve Function

Peripheral nerves may be injured by ischemia of the intraneuronal vasa nervorum, as might be caused by excessive stretch of the nerve or external compression. Nerve conduction studies are useful in the localization and assessment of peripheral nerve dysfunction. Focal demyelination of nerve fibers causes slowing of conduction and decreased amplitudes of compound muscle and sensory action potentials. The presence of denervation potentials in skeletal muscle indicates axonal or anterior horn cell damage. Changes in motor unit potentials also arise from reinnervation of skeletal muscle fibers by surviving axons. Electromyographic testing is helpful in determining the etiology of neurologic dysfunction that may occur after surgery and provides assessment of whether reinnervation has taken place or not.⁵

The Action Potential

Electrical potentials exist across nearly all cell membranes, reflecting principally the difference in transmembrane concentrations of sodium and potassium ions. This unequal distribution of ions is created and maintained by the membrane-bound enzyme sodium-potassium adenosine triphosphatase, sometimes called the sodium-potassium pump. The sodium-potassium pump transfers three sodium ions out of the cell in exchange for two potassium ions brought into the cell. This causes a net transfer of positive charges out of the cell. The resulting voltage difference across the cell membrane is called the *resting membrane potential*. The cytoplasm is electrically negative (typically -60 to -80 mV) relative to the extracellular fluid (Figure 3.2).⁶

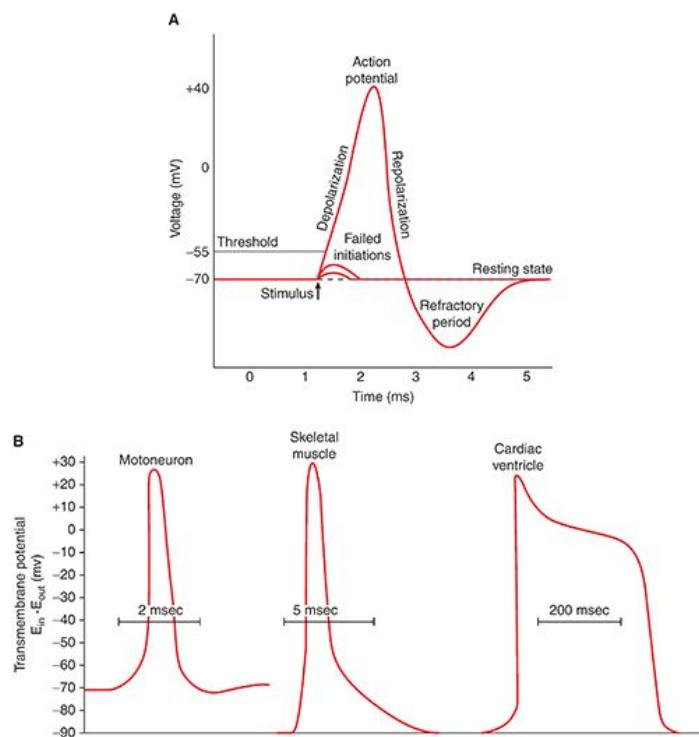


FIGURE 3.2 The elements of the action potential (A). The transmembrane potential and duration of the action potential varies with the tissue site (B). From Berne RM, Levy MN, Koeppen B, et al. Physiology. 5th ed. St Louis, MO: Mosby; 2004. Reprinted with permission from Bruce M. Koeppen, MD.

When channels open to specific ions, the ions generally flow in the direction of their concentration gradients. An action potential is the rapid change in transmembrane potential due to the opening of sodium channels (*depolarization*) and rapid influx of sodium ions down the concentration gradient, reversing the net

negative charge within the cell. The membrane resting potential is restored by the closing of the sodium channels and the opening of potassium channels (*repolarization*) after the action potential has passed. The outward flux of potassium ions down their concentration gradient restores the net negative charge within the cell. This is discussed in greater detail under “Ion Channels” section in the following text.

Propagation of Action Potentials

Propagation of action potentials along the entire length of a nerve axon is the basis of rapid signal transmission along nerve cells. The size and shape of the action potential varies among excitable tissues.⁶

Action potentials are conducted along nerve or muscle fibers by local current flow that produces depolarization of adjacent areas of the cell membrane. These propagated action potentials can travel in both directions along the entire extent of the fiber. The transmission of the depolarization process along nerve or muscle fibers is called a *nerve or muscle impulse*. The entire action potential usually occurs in less than 1 millisecond.

During much of the action potential, the cell membrane is completely refractory to further stimulation. This is termed the *absolute refractory period* and is due to the presence of a large fraction of inactivated sodium ion channels. During the last portion of the action potential, a stronger than normal stimulus can evoke a second action potential. This “relative refractory period” reflects the need to activate a critical number of sodium ion channels to trigger an action potential.

The action potential is dynamic, which is difficult to illustrate with a static textbook image. We encourage the motivated reader to search for the text “action potential animation” on the Internet. There are many high-quality animations of the action potential that dynamically display how it propagates.

Ion Channel Evaluation

Patch clamp electrophysiology can be used to study ion channel functions. In patch clamping, an electrode is placed on the cell surface and suction applied to create a tight seal. This electrode is able to control either the voltage or the current. Current flowing through individual ion channels are measured by clamping or maintaining the voltage of a cell membrane. The membrane potential can be measured by clamping the current.⁷ Currents carried through different types of channels can be isolated by the use of specific inhibitors. For example, tetraethylammonium blocks many types of potassium ion channels, whereas tetrodotoxin blocks many types of sodium ion channels. Patch clamping is a useful technique to characterize ion channels and to analyze the effects of pharmacologic interventions.⁸ Much that is known about the actions of anesthetics on individual ion channels has been learned using these methods.

Abnormal Action Potentials

A deficiency of calcium ions in the extracellular fluid (hypocalcemia) prevents the sodium channels from closing between action potentials. The resulting continuous leak of sodium contributes to sustained depolarization or repetitive firing of cell membranes (tetany). Conversely, high calcium ion concentrations decrease cell membrane permeability to sodium and thus decrease excitability of nerve membranes. Low potassium ion concentrations in extracellular fluid increase the negativity of the resting membrane potential, resulting in hyperpolarization and decreased cell membrane excitability. Skeletal muscle weakness that accompanies hypokalemia presumably reflects sustained hyperpolarization of skeletal muscle membranes. Local anesthetics block sodium channels and thus decrease permeability of nerve cell membranes to sodium ions, preventing achievement of a threshold potential that is necessary for generation of an action potential. Blockage of cardiac ion channels by local anesthetics or antiarrhythmic agents results in altered conduction of cardiac impulses and myocardial contractility.

Neurotransmitters and Receptors

Neurotransmitters are chemical mediators that are released into the synaptic cleft in response to the arrival of an action potential at the nerve ending. Neurotransmitter release is voltage dependent and requires the influx of calcium ions into the presynaptic terminals ([Figure 3.3](#)). Synaptic vesicles in the cell body and dendrites of neurons are the sites of continuous synthesis and storage of neurotransmitters. These vesicles may contain

and release more than one neurotransmitter. Neurotransmitters may be excitatory or inhibitory, depending on the ion selectivity of the protein receptor. A postsynaptic receptor may be excited or inhibited, reflecting the existence of both types of receptors in the same postsynaptic neuron. Furthermore, the same neurotransmitter may be inhibitory at one site and excitatory at another. This is particularly applicable to G protein–coupled receptors as the associated G protein determines the polarity of the response. Some neurotransmitters function as neuromodulators or coagonists in that they influence the sensitivity of receptors to other neurotransmitters. For example, glycine is an important coagonist at the *N*-methyl-D-aspartate (NMDA) receptor.

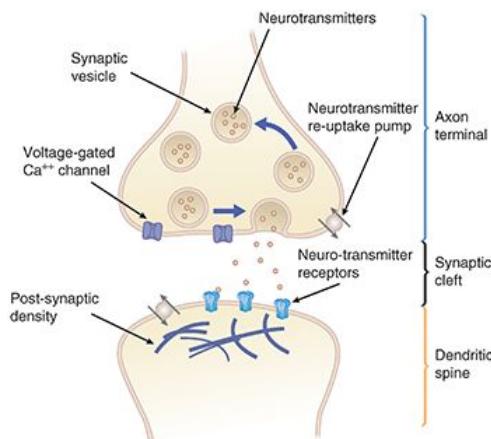


FIGURE 3.3 Basic structure of the synapse. The signal neurotransmitter arrives at the axon terminal, where it causes the release of neurotransmitters into the synapse. These cross the synaptic cleft, where they may or may not result in a propagation of the signal. Many synapses simply render the postsynaptic cell excited or inhibited without actually triggering an action potential.

Volatile anesthetics produce a broad spectrum of actions, as reflected by their ability to modify neurotransmission at presynaptic and postsynaptic loci within the CNS. Volatile anesthetics inhibit excitatory neurotransmission (via NMDA and nicotinic acetylcholine receptors) and enhance the inhibitory neurotransmission (via GABA and glycine receptors).⁹ Some intravenous anesthetics potentiate inhibitory receptors and have the majority of their anesthetic activity through the potentiation of GABAergic and glycinergic transmission, the precise details of which are known.^{10–12} In contrast, the mechanism of volatile effects on analgesia, amnesia, and motor function remain uncertain.¹³ To quote the famous investigator of general anesthetic mechanism, Ted Eger, “Volatile anesthetics inhibit excitatory receptors and activate inhibitory receptors. How do they know?”¹⁴

The list of chemical mediators functioning as excitatory or inhibitory neurotransmitters continues to increase ([Table 3.2](#)). Glutamate is the major excitatory neurotransmitter in the CNS, whereas GABA is the major inhibitory neurotransmitter. Acetylcholine, dopamine, histamine, and norepinephrine are widely distributed and play important roles in sleep pathways that are impacted upon by general anesthetics.¹⁵ Neuromodulators coexist in presynaptic terminals with neurotransmitters but do not themselves cause substantive voltage or conductance changes in postsynaptic cell membranes. They can, however, amplify, prolong, decrease, or shorten the postsynaptic response to selected neurotransmitters.

TABLE 3.2
Chemicals that act at synapses as neurotransmitters
Glutamate
Acetylcholine
Norepinephrine
Glycine
Endorphins

Serotonin
Histamine
Oxytocin
Cholecystokinin
Gastrin
γ -Aminobutyric acid
Dopamine
Epinephrine
Substance P
Vasopressin
Prolactin
Vasoactive intestinal peptide
Glucagon

Receptors can be classified by their cellular localization. Receptors on the cell membrane transduce signals by binding the extracellular molecules and converting this information into an intracellular action that alters target cell function. Most signaling molecules are hydrophobic and interact with cell surface receptors that are directly or indirectly coupled to effector molecules. There are three classes of cell surface receptors as defined by their signal transduction mechanisms: **enzyme-linked transmembrane receptors**, **guanine nucleotide-binding protein (“G protein”) coupled receptors** and **ligand-gated ion channels**.

G protein-coupled receptors in the plasma membrane exert their effects by coupling to specific intracellular G proteins. The binding of the receptor to the ligand activates the G protein, which then activates or inhibits an enzyme, ion channel, or other target. G protein-coupled receptors consist of three separate components: a receptor protein, three guanine nucleotide binding proteins (G proteins α , β , and γ), and an effector mechanism.³ The G protein-coupled receptor consists of a single protein with seven transmembrane spanning domains. Binding of an extracellular ligand to the G protein-coupled receptor triggers a conformational change of the protein. That change causes activation of the G_α protein coupled to the interior portion of the receptor.

A number of different isoforms of G protein subunits (α , β , γ) are present and mediate stimulation, promoting a specific enzymatic reaction within the cell or inhibition, depressing a specific enzymatic reaction. For example, β -adrenergic receptors couple with stimulatory $G_{\alpha s}$ proteins and increase the activity of adenylyl cyclase (also called adenylate cyclase). Opioid receptors associate with inhibitory $G_{\alpha i}$ proteins that decrease the activity of adenylyl cyclase. By regulating the level of activity of adenylyl cyclase, the β -adrenergic and opioid receptors modulate the internal level of cyclic adenosine monophosphate (cAMP), which functions as an intercellular second messenger ([Figure 3.4](#)).

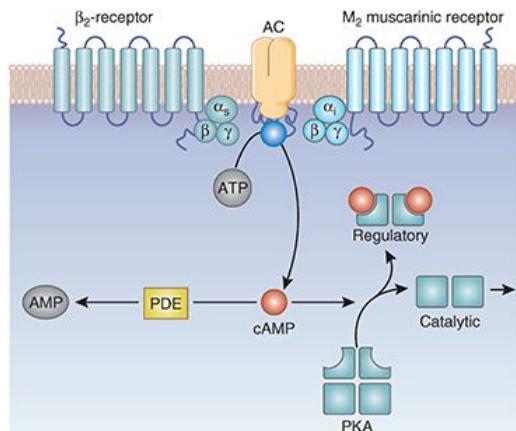


FIGURE 3.4 Schematic showing G protein–coupled receptors, the β_2 adrenergic receptor, which upregulates adenylyl cyclase, and the M_2 muscarinic receptor, which downregulates adenylyl cyclase (AC). The effects of these G protein–coupled receptors are then mediated through the intercellular concentration of cyclic adenosine monophosphate (cAMP). Abbreviations: AMP, adenosine monophosphate; ATP, adenosine triphosphate; PDE, phosphodiesterase; PKA, protein kinase A.

G protein–coupled receptors constitute the largest family of cell surface receptors. Most hormones and many neurotransmitters interact with G protein–coupled cell-surface receptors to produce the cellular response.¹⁶ The resulting response is often a change in transmembrane voltage thus neuronal excitability and the likelihood of response to a stimulus. There is great diversity in the number of G protein–coupled receptors for the same ligand. G protein receptors can couple to more than one G protein and many receptors can couple to the same G protein.¹⁷ Examples of hormones and drugs that act through G protein–coupled receptors, include catecholamines, opioids, anticholinergics, and antihistamines. In contrast to the immediate cellular responses associated with ion channels that manifest in milliseconds, signals mediated by G protein–coupled receptors are involved in functions that operate in seconds to minutes. Some ion channels are also gated by G proteins. These are discussed in the following text with the other ion channels.

Dopamine

Dopamine represents more than 50% of the CNS content of catecholamines, with high concentrations in the basal ganglia. Dopamine can be either inhibitory or excitatory depending on the specific dopaminergic receptor that it activates. Dopamine is important to the reward centers of the brain and plays a key role in addiction and tolerance to anesthetic and analgesic drugs. Dopamine also plays a key role in motor control and abnormalities in dopamine signaling can cause movement disorders as seen in Parkinson disease.

Norepinephrine

Norepinephrine is present in large amounts in the reticular activating system and the hypothalamus, where it plays a key role in natural sleep and analgesia. Neurons responding to norepinephrine send excitatory (through α_1) and inhibitory (through α_2) signals to widespread areas of the brain, including the cerebral cortex. The action of clonidine and dexmedetomidine is mediated by activation of α_2 -adrenergic receptors. The locus coeruleus in the brainstem is the site for the sedative action of dexmedetomidine and the spinal cord is the site for its analgesic effects.¹⁸ Descending noradrenergic fibers that project to the dorsal horn of the spinal cord play an important tonic inhibitory role in pain transmission. These pathways are augmented by epidural clonidine for postoperative and intrapartum analgesia. They are also augmented by serotonin norepinephrine reuptake inhibitors such as duloxetine and venlafaxine used in pain management as analgesic adjuvants.

Substance P

Substance P is an excitatory neurotransmitter coreleased by terminals of pain fibers that synapse in the substantia gelatinosa of the spinal cord. It is found with glutamate in primary afferents and activates the neurokinin 1 G protein–coupled receptor. Its release is not only important to acute pain mediation but also to sustained inflammatory pain. In the mediation of neurogenic inflammation, substance P induces expression of many cytokines that further augment release of substance P and upregulate expression of the neurokinin 1 receptor in a positive feedback response.¹⁹ The neurokinin 1 receptor is also involved in the manifestation of nausea and vomiting after anesthesia, and neurokinin 1 receptor antagonists such as aprepitant are used in its treatment.^{20,21}

Endorphins

Endorphins are endogenous opioid peptide agonists that are secreted by nerve terminals in the pituitary, thalamus, hypothalamus, brainstem, and spinal cord. Endorphins act through the μ -opioid receptor, the same receptor responsible for the effects of administered opioids. Endorphins are secreted after exercise and during

pain and anxiety. They facilitate dopamine release and activate inhibitory pain pathways.²² Endogenous opioids play important roles in many bodily functions including tolerance and dependence, stress, learning and memory, hunger, and the desire for alcohol, drugs, and sexual activity.

Metabotropic Serotonin Receptors

Serotonin (5-HT) is present in high concentrations in the brain, where it acts on both ligand-gated ion channels and G protein-coupled receptors. Many drugs for depression augment activation of serotonin receptors as do many other perioperative medications. Particularly in the setting of anesthesia, consideration of the potential for serotonin syndrome is important.

Histamine

Histamine is present in high concentrations in the hypothalamus and the reticular activating system. Histaminergic neurons present in the tuberomammillary nucleus of the hypothalamus are active during the wake cycle. The sleep promoting properties of antihistamine drugs that cross the blood-brain barrier are due to inhibition of H₁ G protein-coupled receptors.

Ion Channels

The normal resting membrane potential is -60 to -80 mV, with the interior of the cell negative relative to the extracellular fluid. The lipid bilayer is mostly impermeable to ions, which must pass in and out of the cell through ion channels. As discussed earlier, if the flux of ions makes the inside of the cell more negative ("hyperpolarized"), then it is harder for the cell to initiate an action potential. If the flux of ions makes the inside of the cell less negative ("depolarized"), then it is easier for the cell to initiate an action potential.

When ion channels open, ions usually flow in the direction favored by their concentration gradient. Extracellular concentrations of sodium, calcium, and chloride greatly exceed intracellular concentrations, and thus, these ions flow into cells when the appropriate ion channel opens. Some ion channels are restricted to the passage of certain ions. Intracellular concentrations of potassium greatly exceed extracellular concentrations, and thus, potassium follows out of cells whenever a potassium permeable channel is opened. The inwardly rectifying potassium channel is an exception in that potassium flows into the cell, opposite the concentration gradient, in response to the electrical gradient. These channels play an important role in cellular excitability and potassium homeostasis.

When sodium flows into a cell, it makes the interior less negative. Sodium channels are thus depolarizing. When potassium flows out of a cell, it makes the interior more negative. Therefore, potassium channels are hyperpolarizing. Sodium channels open to conduct action potentials, after which potassium channels open to restore the resting negative potential and terminate the action potential.

When chloride flows into a cell, the interior becomes more negative, or hyperpolarized. Because it is harder for a hyperpolarized cell to initiate an action potential, chloride channels are "inhibitory," at least after birth. When calcium flows into a cell, the interior becomes less negative, or "depolarized." Because it is easier for a depolarized cell to initiate an action potential, calcium channels are "excitatory." Calcium can also act as a second messenger within the cell.

When cell membranes are depolarized (the outside becomes less negative relative to the inside) or the appropriate ligand is present, these ion channels undergo conformational changes, the ion channel opens, and ions pass through. About 10⁴ to 10⁵ ions flow per millisecond per channel, and thousands of channels may open during a single action potential.

As mentioned previously, there are three basic types of ion channels: (1) ligand-gated ion channels (ionotropic receptors), (2) voltage-sensitive ion channels, and (3) ion channels that respond to other types of gating. Rapid synaptic transmission is entirely accomplished through the activation of ligand-gated ion channels, which transmit the signal across the synapse, and voltage-gated ion channels, which propagate action potentials.

Voltage-Gated Ion Channels

Voltage-gated ion channels are complexes of protein subunits that act as switchable portals sensitive to membrane potential through which ions can pass through the cell membrane. They are “voltage-sensitive” because they open and close in response to changes in voltage across cell membranes. Charged portions of the molecule physically move in response to voltage changes to energetically favor the open or closed state of the channel. For example, the sodium channel opens in response to a sudden depolarization, propagating the action potential in nerves. Voltage-gated ion channels are present in neurons, skeletal muscles, cardiac muscle, and endocrine cells. They are often named based on the ion that passes through the channel, for example, sodium, chloride, potassium, and calcium channels.

The voltage-gated sodium channel is of particular interest to anesthesiologists because it is the site of local anesthetic action. Local anesthetics block neural conduction by blocking passage of sodium through the voltage sodium channel.

The human *ether-a-go-go* related gene potassium channel is a voltage-gated inwardly rectifying potassium channel, mostly famous for its association with prolonged QT syndrome. The human *ether-a-go-go* related gene potassium channel is sensitive to many drugs and is responsible for sudden death from drugs that predispose the patient to *torsades de pointes*. It is difficult to provide anesthesia without combining drugs that alter the QTc causing great consternation to pharmacists and the U.S. Food and Drug Administration.²³ Despite this, *torsades de pointes* is extremely uncommon during anesthesia in the setting of normal electrolytes.

Ligand-gated ion channels are channels in the plasma membrane that respond directly to extracellular ligands, rather than require coupling through G proteins ([Figure 3.5](#)).

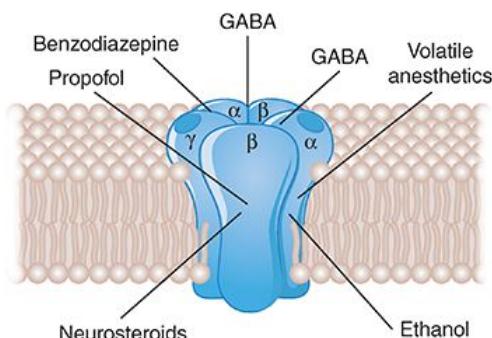


FIGURE 3.5 Schematic of the γ -aminobutyric acid (GABA) type A ligand-gated ion channel. The ligand binds to the external binding domain, modulating the conductance of ions through the central pore. The receptor is a pentamer of two α subunits, two β subunits, and one γ subunit. The binding sites show where several sedatives are known to act. These sedatives increase the flux of chloride through the channel, leading to hyperpolarization of the cell.

Ligand-gated ion channels are involved principally with fast synaptic transmission between excitable cells. Binding of signaling molecules to these receptors causes an immediate conformational change in the ion channels, opening or closing the channel to alter the ion permeability of the plasma membranes and therefore the membrane potential. Ligand-gated ion channels are typically activated by ligands for which they are named. Nicotinic acetylcholine receptors, serotonin receptors (5-HT₃), GABA receptors (GABA_A) (see [Figure 3.5](#)), and glycine receptors are opened in the presence of acetylcholine, serotonin, GABA, and glycine, respectively. Sometimes, the agonist for which the channel is named is not the native agonist. For example, NMDA and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors are named by NMDA and AMPA, the selective nonbiologic agonists that allowed for their specific identification in the laboratory, but the native agonist for both receptors is glutamate. Many general anesthetics act as ligands that may bind at multiple sites on gated ion channels causing inhibitory or excitatory effects.²⁴

Excitatory Ligand-Gated Ion Channels

Excitatory ligand-gated ion channels cause the inside of the cell to become less negative, typically by facilitating the influx of cations into the cell.

Acetylcholine. Acetylcholine is an excitatory neurotransmitter that activates muscarinic and nicotinic receptors in the CNS. Nicotinic acetylcholine receptors are nonspecific cation channels, permitting sodium and in some cases calcium to flow into cells, and potassium to flow out of cells. Because the flow of sodium and calcium is driven both by concentration and electrical gradients, the channel produces a net positive inward flux of cations and is therefore depolarizing (the interior becomes less negative). Nicotinic acetylcholine receptors in the brain are most commonly in a presynaptic location where they act as a “gain control mechanism” to enhance the release of other neurotransmitters. Acetylcholine releasing neurons play an important role in native sleep pathways where acetylcholine mediates arousal.²⁵ The excitatory effect on the CNS mediated through nicotinic ion channels contrasts with the inhibitory effects that are mediated by the G protein-coupled muscarinic acetylcholine receptors in the peripheral parasympathetic nervous system. Nicotinic acetylcholine receptors are also responsible for conducting action potentials to muscles.

While all volatile anesthetics are highly potent inhibitors of the nicotinic acetylcholine receptors,²⁶ direct nicotinic inhibition is not likely responsible for the hypnotic actions of volatile anesthetics because most nicotinic acetylcholine receptors that are expressed in the brain are fully inactivated at anesthetic concentrations that are present on emergence. The inhibition likely occurs through channel blockade, stabilization of close channels, and desensitization. Nicotinic acetylcholine receptors are largely antagonized at volatile anesthetic concentrations and induce immobility rather than mediate the behavioral effects of anesthesia.²⁴ Nicotinic acetylcholine muscle subtype ligand-gated ion channels have provided important tools for the early investigation of general anesthetics. Nondepolarizing muscle relaxants work by blocking the acetylcholine binding site. Because these channels cause depolarization, they are excitatory. Volatile anesthetics are inhibitory at muscle type acetylcholine receptors, but they likely play only a small role in muscle relaxation as there is only moderate inhibition at anesthetizing concentrations.

Glutamate. Glutamate is the major excitatory amino acid neurotransmitter in the CNS. Glutamate receptors are nonselective cation channels, permitting sodium and some calcium to flow into cells, and potassium to flow out of cells dependent on their gradient. Because nonspecific cation channels primarily favor net inward flux of cations down the electrical gradient, glutamate receptors are depolarizing and excitatory. Glutamate-responsive receptors are distributed widely in the CNS. Glutamate plays a key role in learning, and memory, central pain transduction, and pathologic processes such as excitotoxic neuronal injury following CNS trauma or ischemia.

Glutamate is released into the synaptic cleft in response to depolarization of the presynaptic nerve terminal. The release of glutamate from presynaptic terminals is a calcium ion-dependent process regulated by multiple types of calcium channels. In common with many other central neurotransmitter systems, the actions of glutamate within the synaptic cleft is tightly controlled and are terminated by high affinity sodium-dependent reuptake of glutamate and modified by activation of presynaptic receptors.

Ionotropic glutamate receptors (NMDA), AMPA, δ , and kainate receptors are ligand-gated ion channels. Glutamate receptors that respond to NMDA are associated with neuropathic pain and opioid tolerance and are blocked by ketamine. The NMDA receptors are highly calcium permeable. Glutamate receptors that respond to AMPA and kainite are involved with fast synaptic transmission and synaptic plasticity, including long-term potentiation. Ionotropic glutamate receptors are involved in many neurologic disease processes including stroke and Alzheimer disease.²⁷ Metabotropic glutamate receptors are transmembrane receptors that are linked to G proteins that modulate intracellular second messengers such as inositol phosphates and cyclic nucleotides.

Serotonin. The serotonin (5-HT₃) receptor is also excitatory, permitting passage of sodium, potassium, and calcium cations as described for the nicotinic acetylcholine receptor. Among other areas, serotonin receptors are located in the chemoreceptor trigger zone, where they are inhibited by ondansetron, granisetron, and other common antiemetic drugs.²⁰

Inhibitory Ligand-Gated Ion Channels

γ -Aminobutyric Acid. GABA is the major inhibitory neurotransmitter in the brain. The chloride channel is constructed from various combinations of five subunits. The channel is formed from the α and β subunits, with or without γ , δ , ϵ , π and θ subunits. When two molecules of GABA bind to the GABA receptor, the ligand-gated chloride channel in the center of the receptor opens allowing chloride ions to enter the cell following their concentration gradient (see [Figure 3.5](#)). This results in hyperpolarization of the cell membrane and inhibition of transduction.²⁷

As mentioned earlier, GABA receptors mediate many of the anesthetic effects of propofol, etomidate, and thiopental, which directly or at some concentrations indirectly open the channel, causing hyperpolarization of the cell. Benzodiazepines also work through GABA receptors but increase the sensitivity of the receptor to exogenous GABA rather than directly opening the ion channel. There is increasing evidence that extrasynaptic GABA receptors are important in volatile anesthetic-induced behavioral responses.²⁸

Glycine. Glycine is the principal inhibitory neurotransmitter in the spinal cord, acting through the glycine receptor to increase chloride ion conductance into the cell, causing hyperpolarization. Glycine receptors are also present in the brain. These channels are involved in many neurologic processes and are modulated by a variety of anesthetic drugs but are not known to be responsible for any specific anesthetic induced behavior.²⁹

Strychnine and tetanus toxin result in seizures because they antagonize the effects of glycine on postsynaptic inhibition. Visual disturbances after transurethral resection of the prostate in which glycine is the irrigating solution may reflect the role of this substance as an inhibitory neurotransmitter in the retina.³⁰ Amplitude and latency of visual evoked potentials are triggered by infusions of glycine.³¹

G Protein-Gated Ion Channels

Some ion channels are directly gated by G proteins ([Figure 3.6](#)). G protein-gated potassium channels are the most well studied of the G protein-regulated ion channels.³² The first identified G protein-regulated ion channel was the cardiac potassium channel, which is directly regulated by the M₂ muscarinic acetylcholine G protein-coupled receptor.³³ This is one of many inward rectifying potassium channels that share the unusual property of permitting influx of potassium ions into the cell following the electrical gradient, rather than the more typical outward flux of potassium following the ionic concentration gradient. G protein-regulated inwardly rectifying potassium channels, commonly referred to as GIRKs, are regulated by G_{B γ} rather than G_α. In addition to muscarinic acetylcholine, A₁ adenosine, α_2 -adrenergic, D₂ dopamine, opioid, serotonin, and GABA_B receptors are coupled directly to GIRKs.^{32,34}

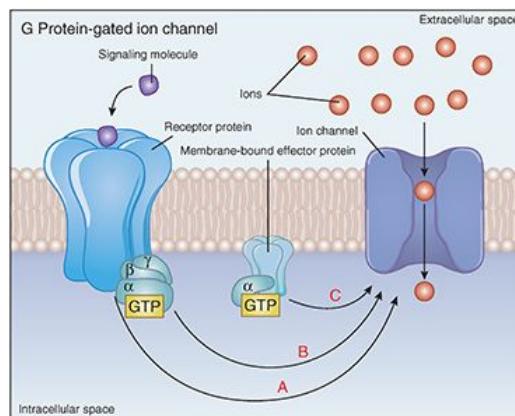


FIGURE 3.6 G protein-gated ion channel. When the signaling molecule binds to the G protein-coupled receptor, the G proteins either directly activate the ion channel (line B for activation by G_α, line C for

activation by $G_{\beta\gamma}$) or activate an intermediary membrane-bound effector protein, which in turn activates the ion channel (line A). Abbreviation: GTP, guanosine triphosphate.

Other-Gated Ion Channels

Other types of ion channel gating include gating by other ions (eg, hydrogen, calcium), second messengers (eg, cAMP, cyclic guanosine monophosphate), and tissue injury (acid, stretch, temperature, cytokines). These mechanisms are outside of the purview of this chapter.

Receptor Concentration

Receptors in cell membranes are not static components of cells. Excess circulating concentrations of ligand often modulate the density of the target receptors in cell membranes. For example, the excessive circulating norepinephrine in patients with pheochromocytoma leads to down regulation of β -adrenergic receptors. Desensitization of receptor responsiveness is the waning of a physiologic response over time despite the presence of a constant stimulus.¹⁶ Drug-induced antagonism of receptors results in an increased density of receptors in cell membranes (upregulation). Abrupt discontinuation of the antagonist can result in an exaggerated response to the endogenous agonist. This is one reason that most cardiovascular medicines should be continued throughout the perioperative period. In contrast, prolonged exposure to high-dose exogenous opioids results in receptor desensitization and internalization that can take significant time to recover. Tolerance to long-term opioid use results from related mechanisms and can take significant time to reverse.³⁵

Receptor Diseases

Numerous diseases are associated with receptor dysfunction.³⁶ For example, failure of parathyroid hormone and arginine vasopressin to produce increases in cAMP in target organs manifests as pseudohypoparathyroidism and nephrogenic diabetes insipidus, respectively. Graves disease and myasthenia gravis reflect development of antibodies against thyroid-stimulating hormone and nicotinic acetylcholine receptors, respectively.

The Synapse

Structure

The synapse functions as a diode that transmits the energy of an action potential from the presynaptic membrane to the postsynaptic membrane across the synaptic cleft ([Figure 3.7](#)). The presynaptic membrane contains the vesicles of neurotransmitter and the reuptake pump that returns the neurotransmitter to the presynaptic axoplasm following neurotransmitter release. It also contains the voltage-gated calcium channel and other channels and receptors that modulate neurotransmitter release. The reuptake pump is also important to modulate postsynaptic excitation and desensitization. Synaptic transmission starts when an afferent action potential arrives at the voltage-gated calcium channel.

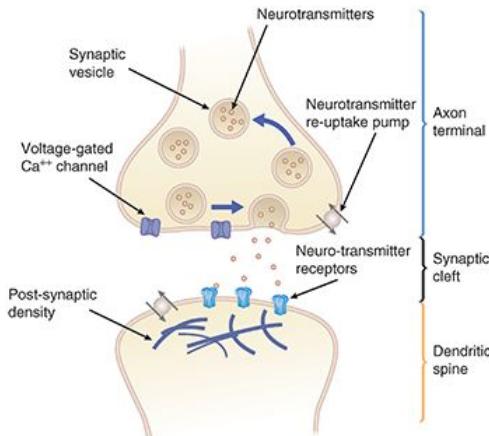


FIGURE 3.7 Structure of the synapse. Axons typically have many synapses, not just the single synapse, implied by the conventional typical rendition in the following text. The presynaptic membrane encloses the synaptic vesicles that contain the neurotransmitters, the reuptake pump that removes the neurotransmitter following synaptic transmission, and the voltage-gated calcium channel that responds to the incoming action potential. The ligand-gated receptors in the postsynaptic membrane trigger an efferent action potential. The postsynaptic density contains multiple proteins and receptors, and appears responsible for organizing the structure of the receptors on the synapse.

The depolarization of the presynaptic neuron permits the influx of calcium ions through the voltage-gated calcium channel. Calcium ions bind to specialized proteins called the release apparatus on axonal and vesicular membranes. Calcium triggers the fusion of the vesicle to the cell membrane and the release of the neurotransmitter into the synaptic cleft through exocytosis, resulting in the extrusion of the contents of the synaptic vesicles. Calcium in the extracellular fluid is essential to the release of neurotransmitters in response to an action potential. The effect of calcium is antagonized by magnesium. Maintenance of extracellular calcium and magnesium concentration is critical during anesthesia to protect both autonomic and CNS homeostasis.

The neurotransmitter in the cleft binds to receptors in the postsynaptic membrane. This binding initiates an efferent action potential in the dendrite or cell body of the efferent nerve, which is then propagated. Immediately distal to the postsynaptic membrane is the postsynaptic density. The postsynaptic density contains a variety of receptors, enzymes, and structural proteins responsible for maintaining synapse homeostasis. The earlier description of “typical synapse” is simplistic and does not consider the enormous variation that underlies the complexity of behavior or synaptic plasticity. More detail can be considered in reviews.^{37,38}

Synaptic Fatigue

Synaptic fatigue is a decrease in the number of discharges by the postsynaptic membrane when excitatory synapses are repetitively and rapidly stimulated. For example, synaptic fatigue decreases excessive excitability of the brain as may accompany a seizure, thus acting as a protective mechanism against excessive neuronal activity. The mechanism of synaptic fatigue is presumed to be exhaustion of the stores of neurotransmitter in the synaptic vesicles. Synaptic fatigue is unmasked at the neuromuscular junction in myasthenia gravis when the enormous reserve for neuromuscular transmission is limited by either pre- or postsynaptic autoimmune damage.

Posttetanic Facilitation

Posttetanic facilitation is increased responsiveness of the postsynaptic neuron to stimulation after a rest period that was preceded by repetitive stimulation of an excitatory synapse. This phenomenon reflects increased release of neurotransmitters due to a short-term increase in the concentration of calcium near the presynaptic apparatus.

Factors That Influence Neuron Responsiveness

Neurons are highly sensitive to changes in the pH of the surrounding interstitial fluids. For example, alkalosis enhances neuron excitability. Voluntary hyperventilation can evoke a seizure in a susceptible individual. Conversely, acidosis depresses neuron excitability, with a decrease in arterial pH to 7.0 potentially causing coma. Hypoxia can cause total refractoriness in neurons as reflected by the almost immediate onset of unconsciousness following cessation of cerebral blood flow. This response is in part protective because the metabolic activity of inactive neurons is an order of magnitude less than that of active neurons. The awake resting brain uses 20% to 25% of the body's total available energy, mostly in the form of glucose.³⁹

Central Nervous System

The brain, brainstem, and spinal cord constitute the CNS. The brain is a complex collection of neural networks that regulate their own and each other's activity. Activity within the CNS reflects a balance between excitatory and inhibitory influences, a homeostasis that is normally maintained within relatively narrow limits. Anatomic divisions of the brain reflect the distribution of brain functions (**Figure 3.8**).

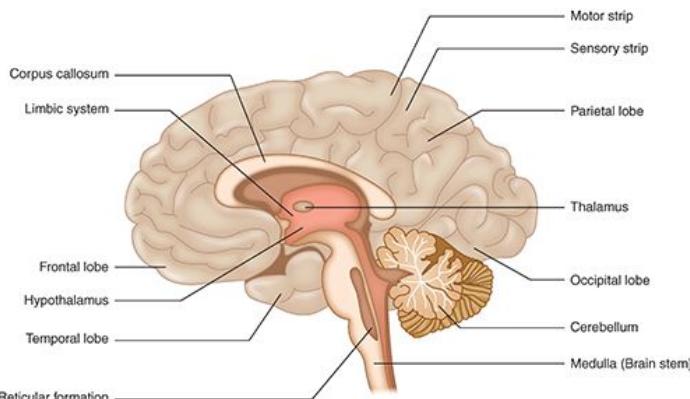


FIGURE 3.8 Brain anatomy.

The brainstem connects the cerebral cortex to the spinal cord and contains most of the nuclei of the cranial nerves and the reticular activating system. The reticular activating system is important for regulation of sleep and wakefulness. The cerebellum arises from the posterior pons and is responsible for coordination of movement, maintenance of body posture, and certain types of motor memory.

The spinal cord extends from the medulla oblongata to the lower lumbar vertebrae. Ascending and descending tracts are located within the white matter of the spinal cord, whereas intersegmental connections and synaptic contacts are concentrated in the gray matter. Sensory information flows into the dorsal portion (posterior) of the gray matter, and motor outflow exits from the ventral (anterior) portion. Preganglionic neurons of the autonomic nervous system are found in the intermediolateral portions of the gray matter.

Cerebral Hemispheres

The two cerebral hemispheres, known as the *cerebral cortex*, constitute the largest division of the human brain. Regions of the cerebral cortex are classically identified as *sensory*, *motor*, *visual*, *auditory*, and *olfactory*, depending on the type of information that is processed. *Frontal*, *temporal*, *parietal*, and *occipital* designate anatomic positions of the cerebral cortex (**Figure 3.9**). For each area of the cerebral cortex, there is a corresponding and connecting area to the thalamus such that stimulation of a small portion of the thalamus activates the corresponding and much larger portion of the cerebral cortex. Indeed, the cerebral cortex is actually an evolutionary outgrowth of the lower regions of the nervous system, especially the thalamus. In embryology and evolution, development the brain develops from the brainstem upward to the cortex.⁴⁰ The functional part of the cerebral cortex is comprised mainly of a 2- to 5-mm layer of neurons covering the surface of all the convolutions.

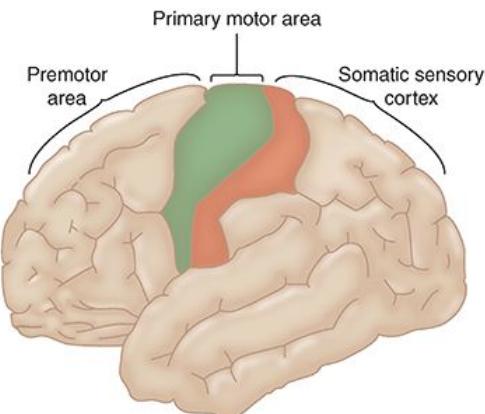


FIGURE 3.9 The sensorimotor cortex consists of the motor cortex, pyramidal (Betz) cells, and somatic sensory cortex.

Anatomy of the Cerebral Cortex

The sensorimotor cortex is the area of the cerebral cortex responsible for receiving sensation from sensory areas of the body and for controlling body movement (see [Figure 3.9](#)).⁴ The premotor cortex is important for controlling the functions of the motor cortex. The motor cortex lies anterior to the central sulcus. Its posterior portion is characterized by the presence of large, pyramid-shaped (pyramidal or Betz) cells.

Topographic Areas

The area of the cerebral cortex to which the peripheral sensory signals are projected from the thalamus is designated the *somesthetic cortex* (see [Figure 3.9](#)).⁴ Each side of the cerebral cortex receives sensory information from the opposite side of the body. The size of these areas is directly proportional to the number of specialized sensory receptors in each respective area of the body. For example, many specialized nerve endings are present in the lips and the thumbs, whereas only a few are present in the skin of the trunk. In the setting of amputation and other trauma, the sensory cortex can remap giving repurposing neurons to nearby healthy areas.⁴¹ While this process underlies rehabilitation after injury, it can be maladaptive and may underlie central pain states.⁴²

The motor cortex is organized into topographic areas corresponding to different regions of the skeletal muscles. The spatial organization is similar to that of the sensory cortex. In general, the size of the area in the motor cortex is proportional to the precision of the skeletal muscle movement required. As such, the digits, lips, tongue, and vocal cords have large representations in humans. The various topographic areas in the motor cortex were originally determined by electrical stimulation of the brain during local anesthesia and observation of the evoked skeletal muscle response. Such stimulation can be used intraoperatively to identify the location of the motor cortex and other areas to avoid damage and to determine function of implants for treatment of diseases such as Parkinson disease and epilepsy.^{43,44} The motor cortex is commonly damaged by loss of blood supply as occurs during a stroke.

Corpus Callosum

The two hemispheres of the cerebral cortex, with the exception of the anterior portions of the temporal lobes, are connected by fibers in the corpus callosum. The anterior portions of the temporal lobes, including the amygdala, are connected by fibers that pass through the anterior commissure. The corpus callosum and anterior commissure make information processed or stored in one hemisphere available to the other hemisphere. Resection of the corpus callosum can cause “split brain syndrome.” A feature is the inability to verbally describe or name an object placed in the left hand, left hemisphere dominance, and inability to understand written language if the writing is presented only to the left visual field. Although the information is transmitted from the left eye to the right cerebral hemisphere, it cannot be transferred to the left for interpretation and verbal output.⁴⁵

Dominant Versus Nondominant Hemisphere

Language function and interpretation is typically localized in the dominant cerebral hemisphere, whereas spatiotemporal relationships (ability to recognize faces) is localized in the nondominant hemisphere. The left hemisphere is dominant in 90% of right-handed individuals and 70% of left-handed individuals.

Memory

The cerebral cortex, especially the medial temporal lobes, serve as a storage and processing site for the formation of memories. The mechanisms for short- and long-term memory are not completely understood but are thought to be encoded through selective synaptic alteration in response to experience. There are several theories to explain the mechanisms of memory formation, many of which involve the modulation of synaptic connectivity. Long-term potentiation occurs when a tetanic stimulation leading to a high-frequency train of action potentials produces a prolonged strengthening of synaptic transmission. Long-term potentiation involves activation of NMDA receptors that produce an influx of postsynaptic calcium. The calcium activates protein kinases.⁴⁶

Short-term memory involves strengthening synaptic connections particularly in the hippocampus. Long-term potentiation of synapses is a major mechanism by which memories are stored in the short-term and for transmission to long-term memories.⁴⁷ Hippocampal function and dysfunction can be tested with neuropsychological tests of learning capacity, proactive interference, immediate recall, delayed recall, and delayed recognition.⁴⁸ Long-term memory is thought to rely on long-term synaptic potentiation mediated by structural changes that produce new proteins. Thus, protein transcription and synaptic remodeling are an essential component of long-term memory. The hippocampus and amygdala are critically involved in creating new long-term memories. However, long-term memories are not actually stored in the hippocampus and amygdala. The actual mechanism by which long-term memories are stored remains a fascinating unsolved puzzle.

Everyone knows from personal experience that repetition is essential to forming long-term memory. There is an old joke about a man asking a fellow pedestrian in New York, “How do you get to Carnegie Hall?” The pedestrian replies, “Practice, practice, practice.” It has been repeatedly demonstrated in animal studies as well that repetition is key to forming long-term memories. Long-term potentiation is the synaptic consequence of repeated stimulation, which is one reason that long-term potentiation is thought to be the fundamental building block of long-term memory.

We also know that memories are transferred from short-term memory to long-term memory. Because the creation of long-term memory requires anatomic changes in the synapse, this transfer requires time. This suggests, and studies confirm, that if the brain is not given adequate time to make this transfer, there will be no transfer from short-term memory to long-term memory. This has direct applicability to the practice of anesthesia. During the provision of general anesthesia, we are vigilant for signs of inadequate anesthesia and intraoperative awareness (discussed further at the end of this section). If a patient has conscious perception of the surgery, this will initially be part of the patient’s short-term memory. Rapid deepening of the anesthesia, for example, by administering a bolus of propofol in response to movement, may prevent transfer of the recall from short-term memory to the long-term memory, and the patient will be amnestic. Conversely, if the patient is paralyzed and is awake for many minutes without the anesthesiologist being aware of the situation, then there has been adequate time for transfer of the short-term memory to long-term memory. Movement inhibition requires higher concentrations of anesthetic than amnesia.⁴⁹ This may explain why targeting the *minimum anesthetic concentration* (MAC) that prevents immobility allows for an extremely low probability of memory under anesthesia.

Because the neural substrate of memory is not well understood, memory is often discussed from a psychological point of view. Memories typically involve multiple senses (sight, hearing, touch), emotions (fear, satisfaction, pleasure, anger), and cognitive assessment (“I remember thinking that . . . ”). These are thought to be held together in a facilitated circuit that has been called a memory engram or memory trace. The pieces of the engram are consolidated through hypothalamic circuitry. The memory engram is reinforced with every subsequent recall of the memory.⁵⁰ An important feature of the process of consolidation is that long-term memory is encoded into different categories. New memories are not stored randomly in the brain

but seem to be associated with previously encoded and similar information. This permits scanning of memory to retrieve desired information at a later date. We also know that memory scanning is often a subconscious process. This is confirmed by the daily experience of struggling to recall a fact or event, only to have the memory suddenly jump into our consciousness hours later.

Awareness and Recall During Anesthesia

Awareness or explicit memory during anesthesia is a dreaded complication. Memory may be considered to be conscious (explicit) or unconscious (implicit). Conscious memory includes spontaneous recall and recognition memory, both of which occur with the aid of a specific cue. Unconscious memory is manifest by altered performance or behavior due to experiences that are not consciously remembered. General anesthesia at an adequate concentration abolishes conscious memory, but the extent to which it also abolishes unconscious memory is controversial and dependent of the type of anesthesia used. The incidence of conscious recall of intraoperative events is rare and the development of posttraumatic stress disorder is even more uncommon. The incidence of awareness with recall (conscious memory) following general anesthesia in some settings where maintenance of anesthetic depth is not possible is surprisingly high, estimated at 5 per 1,000.⁵¹ A higher incidence of awareness has been described for major trauma where anesthetic depth is limited by autonomic function and cardiac surgery where opioids have classically been used as a major part of the anesthetic. While they are potent analgesics, opioids alone do not reliable provide amnesia.⁵²

Neuromuscular blocking drugs permit inadequate anesthesia to be administered without obvious patient withdrawal from the noxious stimulus. The use of neuromuscular blockade is a risk factor for awareness under general anesthesia, particularly awareness that is associated with memories of pain and complicated by posttraumatic stress disorder.⁵³ The use of benzodiazepines have been shown to reduce episodes of awareness. As expected, higher doses of volatile anesthetics reduce episodes of awareness when compare to lower doses.⁵¹

Recognizing Awareness

Monitoring patients during general anesthesia for the presence of awareness is challenging. Despite a variety of monitoring methods, awareness may be difficult to recognize in real time. Indicators of awareness (heart rate, blood pressure, and skeletal muscle movement) are often masked by anesthetic and adjuvant drugs (β -adrenergic blockers, opioids) and/or neuromuscular-blocking drugs. Several monitors, based on analysis of electroencephalogram (EEG) and SSEP patterns have been introduced in hopes of addressing this issue. However, the use of processed EEG anesthetic depth monitoring has not been consistently shown to reduce the risk of awareness.⁵¹

Postoperative Cognitive Dysfunction

Cognitive impairment including impaired memory and perception can occur after surgery and anesthesia. Postoperative cognitive dysfunction persisting after 3 months has been described in 10% of elderly patients receiving general anesthesia for noncardiac surgery without known arterial hypoxemia or systemic hypotension. Increased age and fewer years of education were associated with postoperative cognitive dysfunction (POCD).⁵⁴ Other studies have identified other possible risk factors including postoperative delirium and the used of sedative drugs.⁵⁵ Current recommended perioperative neurocognitive disorders as an inclusive nomenclature for cognitive impairment identified in the preoperative or postoperative period that may include worsening of cognitive decline diagnosed before operation, an acute event (postoperative **delirium**), and cognitive decline diagnosed up to 30 days after the procedure (delayed neurocognitive recovery) and up to 12 months (postoperative neurocognitive disorder).⁵⁶ Several studies have investigated the neurotoxicity related to anesthesia. Inhaled anesthetics have shown potentiation of the pathologic processes involving amyloid precursor protein that are associated with Alzheimer disease. Increased permeability of the blood–brain barrier, neuroinflammation, and microemboli all may play a role in the development of POCD. It is unclear whether the POCD is caused by anesthetic injury to the aged brain or is caused by the combined effects of surgical trauma, inflammation, social interruption, anesthesia, and other unidentified causes.

Brainstem

Homeostatic life sustaining processes are controlled subconsciously in the brainstem. Examples of subconscious activities of the body regulated by the brainstem include control of systemic blood pressure and breathing in the medulla. The thalamus serves as a relay station for most afferent impulses before they are transmitted to the cerebral cortex. The hypothalamus receives fibers from the thalamus and is also closely modulated by the cerebral cortex.

Limbic System and Hypothalamus

Behavior associated with emotions is primarily a function of structures known as the *limbic system* (hippocampus, basal ganglia) located in the basal regions of the brain. The hypothalamus functions in many of the same roles as the limbic system and is considered by some to be part of the limbic system rather than a separate structure. In addition, the hypothalamus controls many internal conditions of the body, such as core temperature, thirst, and appetite. The great Oxford neurophysiologist Sir Charles Sherrington called the *hypothalamus* the *head ganglion* of the autonomic nervous system. The suprachiasmatic nucleus of the hypothalamus helps to maintain the body clock by secreting melatonin and other mediators according to the circadian rhythm. This nucleus sits just above the optic chiasm and received inputs from the optic nerve that serve to entrain the circadian rhythm to environmental light. At high doses, melatonin and its analogs have properties similar to a general anesthetic.⁵⁷ Some general anesthetics activate a group of hypothalamic neurons near the supraoptic nucleus, consisting of neuroendocrine cells, that potentiate general anesthesia.⁵⁸

Basal Ganglia

The basal ganglia include the caudate nucleus, putamen, globus pallidus, substantia nigra, and subthalamic nucleus. Many of the impulses from basal ganglia are inhibitory mediated by dopamine and GABA. The balance between agonist and antagonist skeletal muscle contractions is an important role of the basal ganglia. A general effect of diffuse excitation of the basal ganglia is inhibition of skeletal muscles, reflecting transmission of inhibitory signals from the basal ganglia to both the motor cortex and the lower brainstem. Therefore, whenever destruction of the basal ganglia occurs, there is associated skeletal muscle rigidity. For example, damage to the caudate and putamen nuclei that normally secrete GABA results in both choreiform random and continuous uncontrolled movements. Destruction of the substantia nigra and loss of dopaminergic neurons results in a predominance of the excitatory neurotransmitter acetylcholine, manifesting as the skeletal muscle rigidity of Parkinson disease. Indeed, dopamine precursors or anticholinergic drugs are used in the treatment of Parkinson disease in an attempt to restore the balance between excitatory and inhibitory impulses traveling from the basal ganglia.

Reticular Activating System

The reticular activating system is a polysynaptic pathway that is intimately concerned with electrical activity of the cerebral cortex. Neurons of the reticular activating system are both excitatory and inhibitory. The reticular activating system determines the overall level of CNS activity, including nuclei important in determining wakefulness and sleep. Selective activation of certain areas of the cerebral cortex by the reticular activating system is crucial for direction of attention and certain aspects of mental activity. Injected and inhaled anesthetics exert some of their sedative effects through interaction with the brainstem and midbrain nuclei that mediate arousal and sleep.⁵⁹ This is not to say that general anesthesia is equivalent to sleep. While the EEG response to many anesthetics resembles deep slow-wave sleep, a key difference is that afferent stimulation does not cause arousal.

Slow-Wave Sleep

Most of the sleep that occurs each night is slow-wave sleep. The EEG is characterized by the presence of high-voltage delta waves occurring at a frequency of <4 cycles per second. Presumably, decreased activity of the reticular activating system that accompanies sleep permits an unmasking of this inherent rhythm in the cerebral cortex. Slow-wave sleep is restful and devoid of dreams. During slow-wave sleep, sympathetic nervous system activity decreases, parasympathetic nervous system activity increases, and skeletal muscle

tone is greatly decreased. As a result, there is a 10% to 30% decrease in systemic blood pressure, heart rate, breathing frequency, and basal metabolic rate.

Desynchronized Sleep

Periods of desynchronized sleep typically occur for 5 to 20 minutes during each 90 minutes of sleep. These periods tend to be shortest when the person is extremely tired. This form of sleep is characterized by active dreaming, irregular heart rate and breathing, and a desynchronized pattern of low-voltage beta waves on the EEG similar to those that occur during wakefulness. This brain wave pattern emphasizes that desynchronized sleep is associated with an active cerebral cortex, but this activity does not permit persons to be aware of their surroundings and thus be awake. Despite the inhibition of skeletal muscle activity, the eyes are an exception, exhibiting rapid movements. For this reason, desynchronized sleep is also referred to as *paradoxical sleep* or *rapid eye movement (REM) sleep*.

Cerebellum

The cerebellum operates subconsciously to monitor and elicit corrective responses in motor activity caused by stimulation of other parts of the brain and spinal cord. Rapid repetitive skeletal muscle activities, such as typing, playing musical instruments, and running, require intact function of the cerebellum. Loss of function of the cerebellum causes incoordination of fine skeletal muscle activities even though paralysis of the skeletal muscles does not occur. The cerebellum is also important in the maintenance of equilibrium and postural adjustments of the body.

Dysfunction of the Cerebellum

In the absence of cerebellar function, a person cannot predict prospectively how far movements will go. This results in overshoot of the intended mark (past pointing). This overshoot is known as *dysmetria*, and the resulting incoordinate movements are called *ataxia*. Dysarthria is present when rapid and orderly succession of skeletal muscle movements of the larynx, mouth, and chest do not occur. Failure of the cerebellum to dampen skeletal muscle movements results in intention tremor when a person performs a voluntary act. Cerebellar nystagmus is associated with loss of equilibrium, presumably because of dysfunction of the pathways that pass through the cerebellum from the semicircular canals. In the presence of cerebellar disease, a person is unable to activate antagonist skeletal muscles that prevent a certain portion of the body from moving unexpectedly in an unwanted direction. For example, a person's arm that was previously contracted but restrained by another person will move back rapidly when it is released rather than automatically remain in place.

Spinal Cord

The spinal cord extends from the medulla oblongata to the lower border of the first and, occasionally, the second lumbar vertebra. Below the spinal cord, the vertebral canal is filled by the roots of the lumbar and sacral nerves, which are collectively known as the *cauda equina* (the tail of a horse). The spinal cord is composed of gray and white matter, spinal nerves, and covering membranes.

Gray Matter

The gray matter of the spinal cord functions as the initial processor of incoming sensory signals from peripheral somatic receptors and as a relay station to send these signals to the brain.

In addition, this area of the spinal cord is the site for final processing of motor signals that are being transmitted downward from the brain to skeletal muscles. Anatomically, the gray matter of the spinal cord is divided into anterior, lateral, and dorsal horns consisting of nine separate laminae that are H shaped when viewed in cross-section ([Figure 3.10](#)). The anterior horn is the location of alpha and gamma motor neurons that give rise to nerve fibers that leave the spinal cord via the anterior (ventral) nerve roots and innervate skeletal muscles. Cells of Renshaw are intermediary neurons in the anterior horn, providing nerve fibers that synapse in the gray matter with anterior motor neurons. These cells inhibit the action of anterior motor neurons to limit excessive activity. Cells of the preganglionic neurons of the sympathetic nervous system are

located lateral to the thoracolumbar portions of the spinal cord. Cells of the intermediate neurons located in the portion of the dorsal horns of the spinal cord known as the *substancia gelatinosa* (laminae II-III) transmit afferent tactile, temperature, and pain impulses to the spinothalamic tract. The dorsal horn serves as a gate where impulses in sensory nerve fibers are translated into impulses in ascending tracts. There is evidence for a form of memory in the dorsal horn of the spinal cord that is evoked by intense stimulation. Resulting increases in intracellular calcium set into motion long lasting changes that are associated with central sensitization and result in increased sensitivity to subsequent inoffensive stimuli and may underly some types of chronic pain.⁶⁰

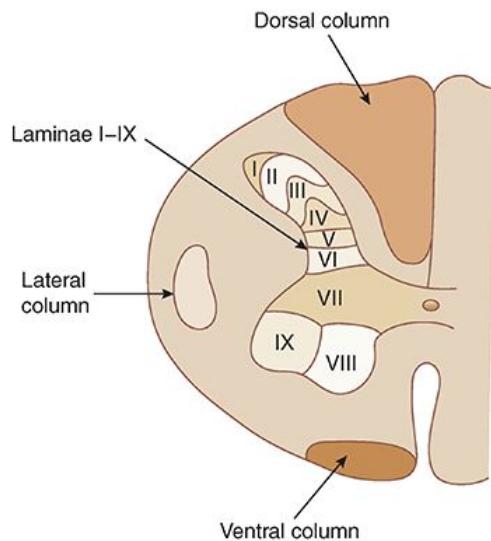


FIGURE 3.10 Schematic diagram of a cross-section of the spinal cord depicting anatomic laminae I to IX of the spinal cord gray matter and the ascending dorsal, lateral, and ventral sensory columns of the spinal cord white matter.

White Matter

The white matter of the spinal cord is formed by the axons that make up their respective ascending and descending tracts. This area of the spinal cord is divided into dorsal, lateral, and ventral columns (see [Figure 3.10](#)). The dorsal column of the spinal cord is composed of spinothalamic tracts that transmit touch and pain impulses to the brain.

Pyramidal and Extrapyramidal Tracts

A major pathway for transmission of motor signals from the cerebral cortex to the anterior motor neurons of the spinal cord is through the pyramidal (corticospinal) tracts ([Figure 3.11](#)).⁴ All pyramidal tract fibers pass downward through the brainstem and then cross to the opposite side to form the pyramids of the medulla. After crossing the midline at the level of the medulla, these fibers descend in the lateral corticospinal tracts of the spinal cord and terminate on motor neurons in the ventral horn of the spinal cord. A few fibers do not cross to the opposite side of the medulla but rather descend in the ventral corticospinal tracts. In addition to these pyramidal fibers, a large number of collateral fibers pass from the motor cortex into the basal ganglia, forming the extrapyramidal tracts. Extrapyramidal tracts are all those tracts beside the pyramidal tracts that transmit motor impulses from the cerebral cortex to the spinal cord.

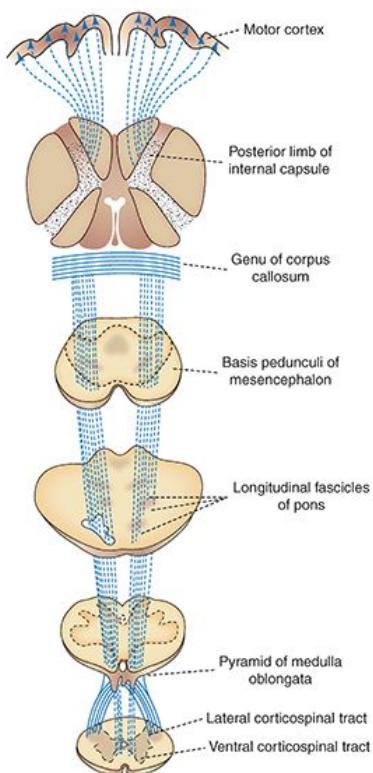


FIGURE 3.11 The pyramidal tracts are major pathways for transmission of motor signals from the cerebral cortex to the spinal cord.

The pyramidal and extrapyramidal tracts have opposing effects on the tone of skeletal muscles. For example, the pyramidal tracts cause continuous facilitation and therefore a tendency to produce increases in skeletal muscle tone. Conversely, the extrapyramidal tracts transmit inhibitory signals through the basal ganglia with resultant inhibition of skeletal muscle tone. Selective or predominant damage to one of these tracts manifests as spasticity or flaccidity.

Babinski Sign

A positive Babinski sign is characterized by upward extension of the first toe and outward fanning of the other toes in response to a firm tactile stimulus applied to the dorsum of the foot. A normal response to the same tactile stimulus is downward motion of all the toes. A positive Babinski sign reflects damage to the pyramidal tracts. Damage to the extrapyramidal tracts does not cause a positive Babinski sign.

Thalamocortical System

The thalamocortical system serves as the pathway for passage of nearly all afferent impulses from the cerebellum; basal ganglia; and visual, auditory, taste, and pain receptors as they pass through the thalamus on the way to the cerebral cortex. Signals from olfactory receptors are the only peripheral sensory signals that do not pass through the thalamus. Overall, thalamocortical integration controls the activity level of the cerebral cortex.

Spinal Nerve

A pair of spinal nerves arises from each of 31 segments of the spinal cord. Spinal nerves are made up of fibers of the anterior and dorsal (posterior) roots. Efferent motor fibers travel in the anterior roots that originate from axons in the anterior and lateral horns of the spinal cord gray matter. Sensory fibers travel in the dorsal nerve roots that originate from axons that arise from cell bodies in the spinal cord ganglia. These cell bodies send branches to the spinal cord and to the periphery. The anterior and dorsal nerve roots each

leave the spinal cord through an individual intervertebral foramen enclosed in a common dural sheath that extends just past the spinal cord ganglia where the spinal nerve originates.

Each spinal nerve innervates a segmental area of skin designated a *dermatome* and an area of skeletal muscle known as a *myotome*. A dermatome map is useful in determining the level of spinal cord injury or level of sensory anesthesia produced by a neuraxial anesthetic (Figure 3.12).⁴ Despite common depictions of dermatomes as having distinct borders, there is extensive overlap between segments. There is greater overlap in areas that are very sensitive. For example, three consecutive dorsal nerve roots need to be interrupted to produce complete denervation of some dermatomes. The scrotum has considerable sensory overlap, with innervation coming from T1 (variable) and L1 to L2 and S2 to S4 despite common depictions on dermatome charts as being limited to sacral innervation.⁶¹ Segmental innervation of myotomes is even less well defined than that of dermatomes, emphasizing that skeletal muscle groups receive innervation from several anterior nerve roots. In these settings, denervation of a dermatome for analgesia may require destruction or overdrive stimulation of several roots that may not be predicted by known dermatomal maps.⁶²

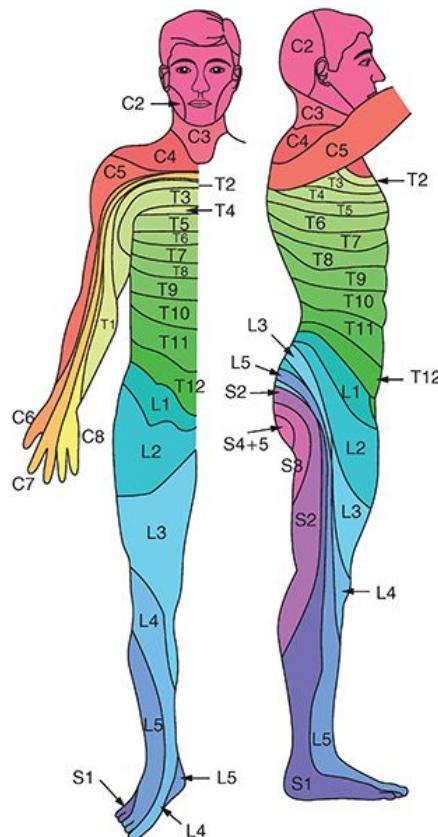


FIGURE 3.12 Dermatome map that may be used to evaluate the level of sensory anesthesia produced by regional anesthesia.

Sensory signals from the periphery are transmitted through spinal nerves into each segment of the spinal cord, resulting in automatic motor responses that occur instantly (muscle stretch reflex, withdrawal reflex) in response to sensory signals. Spinal cord reflexes are important in emptying the bladder and rectum. Segmental temperature reflexes allow localized cutaneous vasodilation or vasoconstriction in response to changes in skin temperature. The function of the spinal cord component of the CNS and spinal cord reflexes is particularly apparent in patients with transection of the spinal cord.

Central Nervous System Membranes

The spinal cord is enveloped by membranes (dura, arachnoid, pia) that are direct continuations of the corresponding membranes surrounding the brain. The dura consists of an inner and an outer layer. The outer periosteal layer in the cranial cavity is the periosteum of the skull, whereas this layer in the spine is the periosteal lining of the spinal cord. The epidural space is located between the inner and outer layers of the dura. The fact that the inner layer of the dura adheres to the margin of the foramen magnum and blends with the periosteal layer meaning that the epidural space does not extend beyond this point. As a result, drugs such as local anesthetics or opioids cannot travel cephalad in the epidural space beyond the foramen magnum. However, there is extensive equilibration between epidural and subarachnoid drug concentrations. Because of this equilibration hydrophilic opioids such as morphine given to the lumbar epidural space may cause delayed respiratory depression in patients at risk. The inner layer of the dura extends as a dural cuff that blends with the perineurium of spinal nerves. The cerebral arachnoid extends as the spinal arachnoid, ending at the second sacral vertebra. The pia is in close contact with the spinal cord.

The plica mediana dorsalis is a connective tissue band that divides the epidural space at the dorsal midline. This band binds the dura mater and the ligamentum flavum at the midline, making it difficult to feel loss of resistance during attempted midline identification of the epidural space. The plica mediana dorsalis may be implicated as a cause of unilateral epidural local anesthesia and has been managed with a bilateral double catheter technique in some settings.⁶³

Autonomic Reflexes

Segmental autonomic reflexes occur in the spinal cord and include changes in vascular tone, diaphoresis, and evacuation of the bladder and colon. Simultaneous excitation of all the segmental reflexes is the mass reflex (denervation hypersensitivity or autonomic hyperreflexia). The mass reflex typically occurs in the presence of spinal cord transection when a painful stimulus is applied to the skin below the level of the spinal cord transection, or following distension of a hollow viscus, such as the bladder or gastrointestinal tract. The principal manifestation of the mass reflex is systemic hypertension due to intense peripheral vasoconstriction, reflecting an inability of vasodilating inhibitory impulses from the CNS to pass beyond the site of spinal cord transection. This can be obviated in patients with high spinal cord lesions with neuraxial or deep general anesthesia that blocks the afferent input. Carotid sinus baroreceptor-mediated reflex bradycardia accompanies the systemic hypertension associated with the mass reflex.

Spinal Shock

Spinal shock is a manifestation of the abrupt loss of spinal cord reflexes that immediately follows transection of the spinal cord. It emphasizes the dependence of spinal cord reflexes on continual tonic discharges from higher centers. The immediate manifestations of spinal shock are hypotension due to loss of vasoconstrictor tone and absence of all skeletal muscle reflexes. Within a few days to weeks, spinal cord neurons gradually regain their intrinsic excitability. Sacral reflexes for control of bladder and colon evacuation are completely suppressed for the first few weeks after spinal cord transection, but these spinal cord reflexes also eventually return although their conscious control does not.

Imaging of the Nervous System

Neuroimaging continues to evolve. Not only can we visualize the anatomy of the brain, skull, and spinal cord but new imaging modalities allow us to visualize physiologic information regarding metabolism and perfusion. Computed tomography (CT) and magnetic resonance imaging (MRI) produce high-resolution cross-sectional images of the brain tissue and clear discrimination between gray and white matter. The CT scans are a fast and reliable way to visualize brain pathology, including detection of intracranial blood flow. The CT angiography uses injected contrast and reconstruction software to provide detailed imaging of the brain's vasculature. The CT perfusion is now widely used to assess acute stroke patients. The CT perfusion assesses cerebral blood flow and can indicate the area of the brain that is still at risk of ischemia. The CT perfusion has resulted in more patients being eligible for management with thrombectomy since we are able to see the areas of brain that are salvageable.

The MRIs have the advantage of imaging without ionizing radiation. A magnetic field and radio waves are used to create the images that are more detailed than CT images. Some patients are not able to undergo MRI because of the presence of artificial cardiac pacemakers, mechanical heart valves, or magnetizable intracranial metal clips.

Positron emission tomography (PET) and single-photon emission CT (SPECT) permit imaging of both structure and functional characteristics (blood flow, metabolism, and concentrations of neurochemicals and receptors) of the brain. The PET scans use radioactive isotopes that are taken up by highly metabolic cells. In combination with CT or MRI, PET scans are useful to assess for location and spread of malignancy.

Cerebral Blood Flow

Cerebral blood flow averages 50 mL/100 g/minute of brain tissue under normal conditions. For an adult, this is equivalent to 750 mL per minute, or about 15% of the resting cardiac output, delivered to an organ that represents only about 2% of the body's mass. The gray matter of the brain has a higher cerebral blood flow (80 mL/100 g/minute) than the white matter (20 mL/100 g/minute). As in most other tissues of the body, cerebral blood flow parallels cerebral metabolic requirements for oxygen (3-5 mL/100 g/minute). Ischemic injury occurs when blood flow decreases below 22 mL/100 g/minute. The cerebral vasculature responds to changes in PaCO_2 and PaO_2 known as vasomotor reactivity. Sympathetic and parasympathetic nerves play little or no role in the regulation of cerebral blood flow ([Figure 3.13](#)). Changes in the PaCO_2 between about 20 and 80 mm Hg produce corresponding linear changes in cerebral blood flow. For example, in this range, a 1-mm Hg increase in the PaCO_2 leads to a 1% to 6% increase in cerebral blood flow ([Table 3.3](#)). The change in blood flow with change in carbon dioxide is only temporary as the vasculature adapts to the chronic elevation of PaCO_2 and the cerebral blood flow will eventually return to normal.⁶³

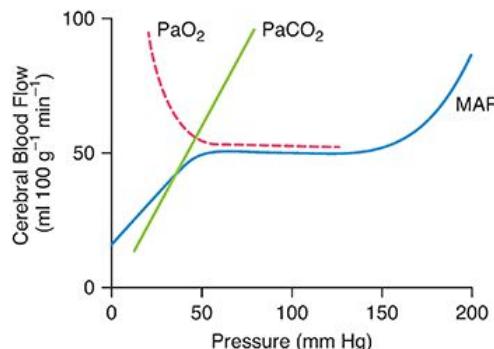


FIGURE 3.13 Cerebral blood flow is influenced by PaO_2 , PaCO_2 , and mean arterial pressure (MAP).

TABLE 3.3

Carbon dioxide and cerebral physiology

Cerebral blood flow (CBF)

Changes 1-2 mL/100 g/minute for each 1 mm Hg change in PaCO_2 between 20 and 80 mm Hg

Slope of the response depends on normocapnic CBF.

CBF returns to baseline over several hours during sustained alterations in PaCO_2 (reflects correction of brain extracellular fluid pH).

Response to hypocapnia not altered by aging if CBF is maintained

Response to changes in PaCO_2 not altered by untreated hypertension

Hypothermia decreases normocapnic CBF and the response of CBF to changes in PaCO_2 .

Cerebral blood volume (CBV)

Changes 0.05 mL/100 g for each 1 mm Hg change in PaCO_2

Returns to baseline during sustained alterations in Paco_2

Cerebral autoregulation

Modest hypercapnia impairs, and marked hypercapnia abolishes.

Hypotension below the lower limit of autoregulation abolishes hypocapnic cerebral vasoconstriction.

Carbon dioxide response and anesthetics

Maintained during inhaled and intravenous anesthetics

Relative response to hypcapnia depends on normocapnic CBF (anesthetics that increase CBF enhance the reduction of CBF by hypcapnia).

Carbon dioxide response in presence of disease or injury

Hypercapnic response intact with hypertension

Hypcapnia response present with brain injury (subarachnoid hemorrhage) but may be attenuated if vasospasm is present

Carbon dioxide increases cerebral blood flow by combining with water in body fluids to form carbonic acid that dissociates to form hydrogen ions. Hydrogen ions produce vasodilation of cerebral vessels that is proportional to the increase in hydrogen ion concentration.

Any other acid that increases hydrogen ion concentration, such as lactic acid, also increases cerebral blood flow. Increased cerebral blood flow in response to increases in Paco_2 serves to carry away excess hydrogen ions that would otherwise greatly depress neuronal activity.

Unlike the continuous response of cerebral blood flow to changes in Paco_2 , the response to PaO_2 is a threshold phenomenon (see [Figure 3.13](#)). If the Paco_2 is maintained, cerebral blood flow begins to increase when the PaO_2 decreases below 30 mm.⁶⁴

Autoregulation

Cerebral blood flow is closely autoregulated between a mean arterial pressure of about 50 and 160 mm Hg (see [Figure 3.13](#)). As a result, changes in systemic blood pressure within this range will not significantly alter cerebral blood flow. Chronic systemic hypertension shifts the autoregulation curve to the right such that decreases in cerebral blood flow may occur at a mean arterial pressure of >50 mm Hg. Autoregulation of cerebral blood flow is attenuated or abolished by hypercapnia, arterial hypoxemia, and volatile anesthetics. Furthermore, autoregulation is often abolished in the area surrounding an acute cerebral infarction. For example, reactivity of blood vessels in areas surrounding cerebral infarcts and tumors is abolished. These blood vessels are maximally vasodilated, presumably reflecting accumulation of acidic metabolic products. As a result, cerebral blood flow to this area is already maximal (luxury perfusion), and changes in Paco_2 have no effect on its local blood flow. If Paco_2 should increase, however, it is theoretically possible that resulting vasodilation in normal blood vessels would shunt blood flow away from the diseased area (intracerebral steal syndrome). Conversely, a decrease in Paco_2 that constricts normal cerebral vessels could divert blood flow to diseased areas (“Robin Hood” phenomenon). Increases in mean arterial pressure above the limits of autoregulation can cause leakage of intravascular fluid through capillary membranes, resulting in cerebral edema. Because the brain is enclosed in a solid vault, the accumulation of edema fluid increases intracranial pressure (ICP) and compresses blood vessels, decreasing cerebral blood flow and leading to destruction of brain tissue. Cerebral autoregulation can be altered by trauma and other diseases.

Electroencephalogram

The EEG is a recording of the brain waves that result from the summed electrical activity in the brain. The intensity of the electrical activity recorded from the surface of the scalp ranges from 0 to 300 μV , and the frequency may exceed 50 cycles per second. The character of the waves greatly depends on the level of activity of the cerebral cortex and the degree of wakefulness. There is a direct relationship between the degree of cerebral activity and the frequency of brain waves. Furthermore, during periods of increased mental

activity, brain waves become asynchronous rather than synchronous, so the voltage decreases despite greater cortical activity.

Classification of Brain Waves

Brain waves are classified as alpha, beta, theta, and delta waves depending on their frequency and amplitude ([Figure 3.14](#)). The classic EEG is a plot of voltage against time, usually recorded by 16 channels on paper moving at 30 mm per second. One page of recording is 10 seconds of data.

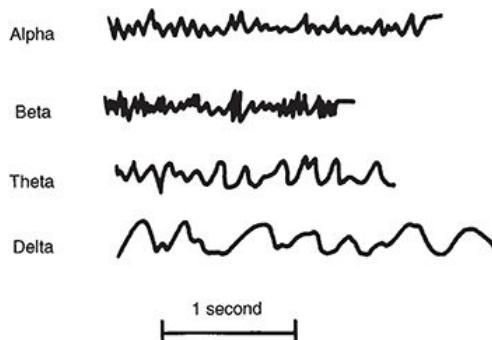


FIGURE 3.14 The electroencephalogram consists of alpha, beta, theta, and delta waves.

Alpha Waves

Alpha waves occur at a frequency of 8 to 12 Hz and a voltage of about 50 μ V. These waves are typical of an awake, resting state of cerebration with the eyes closed. During sleep, alpha waves disappear. Because alpha waves do not occur when the cerebral cortex is not connected to the thalamus, it is assumed these waves result from spontaneous activity in the thalamocortical system.

Beta Waves

Beta waves occur at a frequency of 13 to 30 Hz and a voltage usually of <50 μ V. These high-frequency and low-voltage asynchronous waves replace alpha waves in the presence of increased mental activity or visual stimulation.

Theta Waves

Theta waves occur at a frequency of 4 to 7 Hz. These waves occur in healthy people during sleep and also during general anesthesia.

Delta Waves

Delta waves include all the brain waves with a frequency of less than 4 Hz. These waves occur (1) in deep sleep, (2) during general anesthesia, and (3) in the presence of organic brain disease. Delta waves occur even when the connections of the cerebral cortex to the reticular activating system are severed, indicating these waves originate in the cerebral cortex independently of lower brain structures.

Clinical Uses

The EEG is useful in diagnosing different types of epilepsy and for determining the focus in the brain causing seizures. Brain tumors, which compress surrounding neurons and cause abnormal electrical activity, may be localized using the EEG. Monitoring of the EEG during carotid endarterectomy, cardiopulmonary bypass, or controlled hypotension may provide an early warning of inadequate cerebral blood flow. In this regard, the EEG may be influenced by anesthetic drugs, depth of anesthesia, and hyperventilation of the patient's lungs. Several different monitors of EEG activity use different algorithms designed to take time complex EEG and decompose it into a number that is predictive of anesthetic depth.

Brain Wave Monitors

Numerous quantitative EEG processing techniques have been developed to monitor brain depression during anesthesia including processed EEG and entropy monitors.

Many of these commercial monitors use proprietary algorithms to integrate EEG signals into a simple, intuitive output that can be used by clinicians who are not trained in the relatively complex interpretations of classical EEG. Spectral entropy represents an alternative concept to bispectral analysis for quantifying the EEG. Spectral entropy and response entropy are computed over specific frequency ranges of the EEG. Response entropy includes electromyographic activity. The question of whether processed EEG monitoring results in reduction of intraoperative awareness is controversial, and studies have been inconsistent.

Epilepsy

Epilepsy is characterized by excessive activity of either a part or all of the CNS. A grand mal seizure is characterized by intense neuronal discharges in multiple areas of the cerebral and reticular activating system. These impulses are transmitted to the spinal cord, resulting in alternating skeletal muscle contractions known as *tonic-clonic seizures*. Profound autonomic activity often results in defecation and urination. The grand mal seizure usually lasts from a few seconds to several minutes and is followed by generalized depression of the entire CNS (the postictal state). The EEG during a grand mal seizure reveals high-voltage, synchronous brain wave discharges over the entire cerebral cortex. Synaptic fatigue is a likely mechanism that contributes to spontaneous cessation of a grand mal seizure and postictal depression.

Status epilepticus is present, and electrographic seizures last longer than 5 minutes or when multiple seizures occur without return to baseline in between. Status epilepticus can be convulsive or nonconvulsive and is a neurologic emergency as ongoing epileptiform discharges may cause neuronal injury. Ongoing seizures can result in respiratory failure and metabolic acidosis. The development of status epilepticus from a single seizure involves a complex cascade of events occurring at the molecular level including excessive neurotransmitter release (glutamate), ion channel opening and closing and protein phosphorylation. The next stage involves receptor modulation resulting in a downregulation of GABA and an increase in NMDA and AMPA excitatory receptors. Proconvulsant neuropeptides then exhibit increased expression and inhibitory neuropeptides have reduced expression leading to sustained hyperexcitability and status epilepticus. There are antiepileptic drugs with many different mechanisms of action that are used for management of seizures. Drugs readily available to anesthesiologists include benzodiazepines and propofol, which work at the GABA receptors. Intravenous anesthetics are titrated to suppression of seizure on EEG.⁶⁵ Volatile anesthetics can also be used to control refractory status epilepticus but are not often available outside of the operating room.

Evoked Potentials

Evoked potentials are the electrophysiologic responses of the CNS to sensory, motor, auditory, or visual stimulation. The waveforms resulting from sensory stimulation reflect transmission of impulses through specific sensory pathways. Poststimulus latency is the time in milliseconds from application of the stimulus to a peak in the recorded waveform. The amplitude and latency of evoked potentials may be influenced by a number of events, especially volatile anesthetics. Physiologic parameters such as hypotension, hypothermia, and anemia can also affect the recording of evoked potentials. Evoked potentials are used to monitor spinal cord function during operations near or on the spinal cord and auditory nerve and brainstem function, as during operations on pituitary tumors or other lesions that impinge on the optic nerves or optic chiasm. The modes of sensory stimulation used to produce evoked potentials in the operating room are somatosensory, auditory, and visual.^{66,67} The intraoperative monitoring of evoked potentials is an alternative to wake-up testing during neurosurgery. The motor pathway, supplied by the anterior spinal artery is monitored with motor evoked potentials. The sensory pathway, supplied by the posterior spinal artery, is measured with somatosensory evoked potentials.

Somatosensory Evoked Potentials

Somatosensory evoked potentials are produced by application of a low-voltage electrical current that stimulates a peripheral nerve such as the median nerve at the wrist or the posterior tibial nerve at the ankle. The resulting evoked potentials reflect the integrity of sensory neural pathways from the peripheral nerve to

the somatosensory cortex. Somatosensory stimulation follows the dorsal column pathways of proprioception and vibration. Inhaled anesthetics, especially volatile anesthetics, produce dose-dependent depression of somatosensory evoked potentials (see [Chapter 4](#)). Although less so than volatile anesthetics, morphine and fentanyl also produce depressant effects on somatosensory evoked potentials, with a low-dose continuous infusion of the opioid producing less depression than intermittent injections.⁶⁸ Many anesthetic techniques have been described to optimize the recording of motor and sensory evoked potentials. Total intravenous anesthesia with continuous infusion is often used to maintain a constant level of anesthesia so that any observed changes to the evoked potentials will be less likely due to the anesthesia. Ketamine or etomidate may increase the amplitude of somatosensory evoked potentials (see [Chapter 5](#)).

Motor Evoked Potentials

The use of motor evoked potentials is limited by the fact that their recording requires direct (epidural) or indirect (transosseous) stimulation of the brain or spinal cord.⁶⁹ These evoked potentials reflect the integrity of motor neural pathways from the peripheral nerve to the motor cerebral cortex. Motor evoked potentials are extremely sensitive to depression by anesthetics. Furthermore, it is not possible to monitor motor evoked potentials in the presence of significant drug-induced neuromuscular blockade. During scoliosis surgery or other operations that place spinal cord motor function at risk, the use of motor evoked potentials obviates the need for an intraoperative wake-up test. In many instances, it is useful to monitor both motor and sensory evoked potentials to fully evaluate the functional integrity of both motor and sensory pathways. As an alternative to motor evoked potentials, transcranial motor stimulation may be used to monitor spinal cord function during spinal surgery.

Auditory Evoked Potentials

Auditory evoked potentials arise from brainstem auditory pathways. Volatile anesthetics produce dose-dependent depression of auditory evoked potentials. Auditory evoked potentials may provide an objective electrophysiologic alternative to the clinical assessment of sedation, particularly during brain surgery that may affect the cochlea or brain centers important for hearing.⁷⁰

Visual Evoked Potentials

Visual evoked potentials are produced by flashes from light-emitting diodes that are mounted on goggles placed over the patient's closed eyes. Visual evoked potentials may be useful to monitor the visual pathways during trans sphenoidal or anterior fossa neurosurgical procedures. Volatile anesthetics produce dose-dependent depression of visual evoked potentials, especially above concentrations equivalent to about 0.8 MAC.⁷¹

Cerebrospinal Fluid

Cerebrospinal fluid (CSF) is present in the ventricles of the brain, cisterns around the brain, and subarachnoid space around the brain and spinal cord ([Figure 3.15](#)). The total volume of CSF is normally about 150 mL, and the specific gravity is 1.002 to 1.009. A major function of CSF is to cushion the brain in the cranial cavity. A blow to the head moves the entire brain simultaneously, causing no one portion of the brain to be selectively contorted by the blow. When a blow to the head is particularly severe, it usually does not damage the brain on the ipsilateral side but instead damage manifests on the opposite side. This phenomenon results in a *contrecoup* injury reflecting the vacuum between the brain and skull opposite the blow caused by sudden movement of the brain at this site away from the skull. When the skull is no longer being accelerated by the blow, the vacuum suddenly collapses and the brain strikes the interior of the skull.

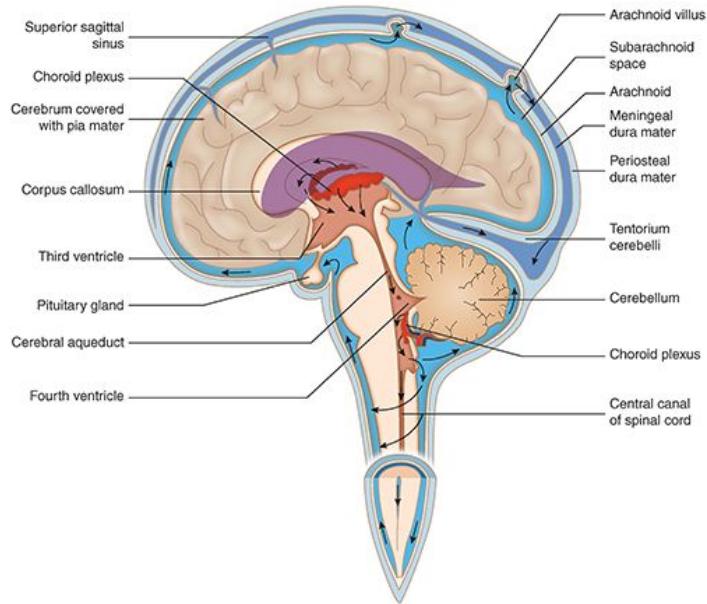


FIGURE 3.15 Cerebral spinal fluid fluxes in and out of the ventricles with the cardiac cycle.

Formation

The choroid plexuses (cauliflower-like growths of blood vessels covered by a thin layer of epithelial cells) in the four cerebral ventricles are the major site of formation of CSF that continually exudes from the surface of the choroid plexus at a rate of about 30 mL per hour. In comparison with other extracellular fluids, the concentration of sodium and chloride in CSF is 7% greater and the concentration of glucose and potassium is 30% and 40% less, respectively. This difference in composition from other extracellular fluids emphasizes that CSF is a choroid secretion and not a simple filtrate from the capillaries. The pH of CSF is closely regulated and maintained at 7.32. Changes in PaCO_2 , but not arterial pH, promptly alter CSF pH, reflecting the ability of carbon dioxide, but not hydrogen ions, to cross the blood–brain barrier easily. As a result, acute respiratory acidosis or alkalosis produce corresponding changes in CSF pH. Active transport of bicarbonate ions eventually returns CSF pH to 7.32, despite the persistence of alterations in arterial pH.

Reabsorption

Almost all the CSF formed each day is reabsorbed into the venous circulation through special structures known as *arachnoid villi* or *granulations*. These villi project the subarachnoid spaces into the venous sinuses of the brain and occasionally into veins of the spinal cord. Arachnoid villi are trabeculae that protrude through venous walls, resulting in highly permeable areas that permit relatively free flow of CSF into the circulation. The magnitude of reabsorption depends on the pressure gradient between the CSF and the venous circulation.

Intracerebral Circulation

The CSF formed in the lateral cerebral ventricles passes into the third ventricle through the foramen of Monro (see [Figure 3.15](#)). From there, CSF passes along the aqueduct of Sylvius into the fourth cerebral ventricle, where still more CSF is formed. It then passes into the cisterna magna through the lateral foramen of Luschka and via a middle foramen of Magendie. From this point, CSF flows through the subarachnoid spaces upward toward the cerebrum, where most of the arachnoid villi are located.

Hydrocephalus

Congenital or acquired obstruction to free circulation of CSF results in hydrocephalus. For example, blockage of the aqueduct of Sylvius results in expansion of the lateral and third cerebral ventricles and compression of

the brain. This type of obstruction producing a noncommunicating type of hydrocephalus is treated by surgical creation of an artificial pathway for flow of CSF between the cerebral ventricular system and the subarachnoid space. Other obstructive hydrocephalus is treated by placing a shunt between the lateral ventricle that drains to a position outside the CNS. The most common type of shunt is a ventricular peritoneal shunt that terminates in the peritoneum. Shunts can also terminate in the pleural space or internal jugular vein. Communicating or nonobstructive hydrocephalus occurs when there is an overproduction or underabsorption of CSF.

Intracranial Pressure

Normal ICP is <15 mm Hg. This pressure is regulated by the rate of CSF formation and resistance to CSF reabsorption through arachnoid villi as determined by venous pressure. In addition, increases in cerebral blood flow, as during inhalation of volatile anesthetics, can cause the ICP to increase because of the concomitant increase in cerebral blood flow and cerebral blood volume.⁷² Systemic blood pressure does not alter ICP within the range of normal autoregulation. Phasic variations in systemic blood pressure, however, are transmitted as variations in ICP. Regulation of global cerebral blood flow is thus particularly important when the brain is near the critical pressure that will result in compression of the brain parenchyma.⁷³

Papilledema

Anatomically, the dura of the brain extends as a sheath around the optic nerve and then connects with the sclera of the eye. Increases in ICP are transmitted to the optic nerve sheath. Increased pressure in the optic sheath impedes blood flow in the retinal veins, leading to increases in the retinal capillary pressure and retinal edema. The tissues of the optic disc are more distensible than the rest of the retina, so the disc becomes edematous and swells into the cavity of the eye. This swelling of the optic disc is termed *papilledema*. Papilledema can be observed with an ophthalmoscope or by using point of care ultrasound to measure the optic nerve sheath diameter.

Blood–Brain Barrier

The blood–brain barrier reflects the impermeability of capillaries in the CNS, including the choroid plexuses, to circulating substances such as electrolytes and exogenous drugs or toxins. The neural and glial cells in the CNS live in a relatively tightly controlled milieu in a healthy state; however, it becomes more porous in the setting of inflammation. The blood–brain barrier is maintained by the tight junction between endothelial cells of brain capillaries. Envelopment of brain capillaries by glial cells further decreases their permeability. The blood–brain barrier is less developed in the neonate and tends to break down in areas of the brain that are irradiated, infected, or compromised by neoplasm. The blood–brain barrier is also relatively permeable in the area around the posterior pituitary and the chemoreceptor trigger zone. It is characterized by active processes mediated by p-glycoprotein transporters. These proteins are of the adenosine triphosphate binding cassette family. Active transport of morphine out of the CNS by a p-glycoprotein transporter is responsible for the >90-minute delay between the plasma peak after a morphine bolus and peak morphine drug effect. Many techniques are being developed to selectively transport drugs across the blood–brain barrier, including targeting intrinsic blood–brain barrier transport proteins and the use of nanoparticles that are too small to be restricted.^{74,75}

Vision

The eye is optically similar to a photographic camera in that it contains a lens system, a variable aperture system (pupil), and light sensitive surface (retina) (**Figure 3.16**).⁷⁶ The lens system of the eye focuses an image on the retina. Relaxation and contraction of the ciliary muscles are responsible for altering the tension of ligaments attached to the lens, causing its refractive power to change. Stimulation of parasympathetic nervous system fibers to the ciliary muscle causes this muscle to relax, which in turn relaxes the ligaments of the lens and increases its refractive power. This increased refractive power allows the eye to focus on objects that are nearby. Interference with this process of accommodation may be noted by patients who have received an anticholinergic drug as part of the pharmacologic reversal of nondepolarizing neuromuscular blockade.

The principal function of the pupil is to increase or decrease the amount of light that enters the eye. For example, the pupil may vary from 1.5 to 8.0 mm in diameter, permitting a 30-fold variation in the amount of light that enters the eye.

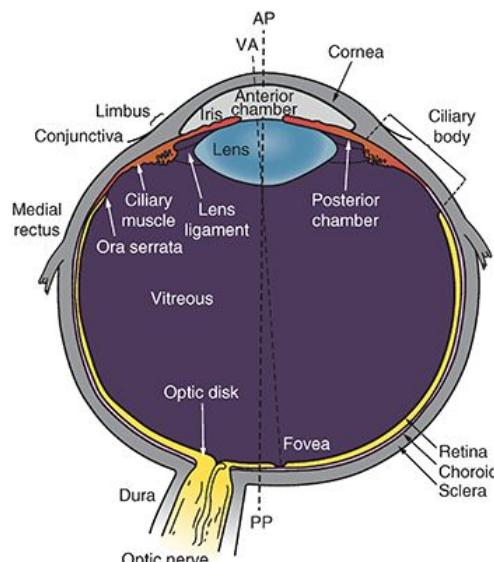


FIGURE 3.16 Schematic diagram of the eye. Abbreviations: AP, anterior pole; PP, posterior pole; VA, visual axis.

Intraocular Pressure

Intraocular pressure is normally 15 to 25 mm Hg. Glaucoma is associated with increased intraocular pressure sufficient to compress retinal artery inflow to the eye, leading to ischemic pain and eventually blindness. When medical control of glaucoma fails, it may be necessary to surgically create an artificial outflow tract for aqueous humor.

Retina

The retina is the light-sensitive portion of the eye containing the cones, which are responsible for color vision, and the rods, which are mainly responsible for vision in the dark. When the cones and rods are stimulated, impulses are transmitted and processed through successive neurons in the retina and optic nerve before reaching the cerebral cortex. The presence of melanin in the pigment layer of the retina prevents reflection of light throughout the globe. Without this pigment, light rays would be reflected in all directions within the globe, causing visual acuity to be impaired. Indeed, albinos, who lack melanin, have greatly decreased visual acuity.

The nutrient blood supply for the retina is largely derived from the central retinal artery, which accompanies the optic nerve. This independent retinal blood supply prevents rapid degeneration of the retina, should it become detached from the pigment epithelium, and allows time for surgical correction of a detached retina. The main arterial supply to the globe and orbital contents is from the ophthalmic artery, which is a branch of the internal carotid artery.⁷⁷

Ischemic Optic Neuropathy

Ischemic optic neuropathy (ION) results from infarction of the optic nerve and is the most frequently reported cause of vision loss following general anesthesia. An ION is classified as *anterior ION* (nonarteritic or arteritic) and *posterior ION*. Arteritic anterior ION is usually not associated with surgery but occurs secondary to temporal arteritis. Nonarteritic anterior ION occurs more often in patients with congenitally small optic discs. It is presumed that the small cross-sectional area of the optic disc results in little room for expansion of optic nerve fibers in response to ischemia-induced edema. Anterior ION associated with surgery

occurs more commonly with cardiac bypass, major vascular, and prone spine operations. Anterior ION results in sudden painless visual disturbances.

Posterior ION has been reported after diverse surgical procedures (prolonged spinal fusion surgery, cardiac operations requiring cardiopulmonary bypass, radical neck surgery), and its etiology appears to be multifactorial. The posterior optic nerve is vulnerable because it lacks overlapping blood supply. Prone positioning decreases venous return and increased intraocular pressure during anesthesia and could contribute to decreases in ocular perfusion pressure.⁷⁸ Head-down or prone position can cause decreased venous return and swelling with reduced perfusion to the optic nerve. Six independent risk factors have been identified for ION with spine surgery including male sex, obesity, the use of a Wilson frame, long operating time, lower colloid to crystalloid ratio for fluid administration, and greater blood loss.⁷⁹

Other Causes of Postoperative Blindness

Cortical blindness, retinal occlusion, and ophthalmic venous obstruction need to be excluded when postoperative blindness occurs. Cortical blindness is characterized by loss of visual sensation with retention of pupillary reaction to light and normal funduscopic examination results. Cortical blindness may be caused by an embolism or cerebral hypoperfusion. A CT or an MRI abnormality in the parietal or occipital lobe confirms the diagnosis. Central retinal artery occlusion presents as painless, monocular blindness caused by a decreased blood supply to the retina. Ophthalmoscopic examination of the eyes with retinal artery occlusion shows a pale edematous retina, a cherry-red spot at the fovea, and platelet-fibrin or cholesterol emboli in the narrowed retinal arteries. The pupillary light reflex will be absent. Obstruction of venous drainage from the eye may occur intraoperatively when patient positioning results in external pressure on the eyes.⁷⁹

Visual Pathway

Impulses from the retina pass backward through the optic nerve (Figure 3.17).⁷⁶ The macula is a small area in the center of the retina that is composed mainly of cones to permit detailed vision. The fovea is the central portion of the macula and is the site of the clearest vision. At the optic chiasm, all the fibers from the nasal halves of the retina cross to the opposite side to join fibers from the opposite temporal retina to form the optic tracts. Fibers of the optic tract synapse in the lateral geniculate body of the thalamus before passing into the visual (occipital) area of the cerebral cortex. Specific points of the retina connect with specific points of the visual cortex, which results in the detection of lines, borders, and colors.

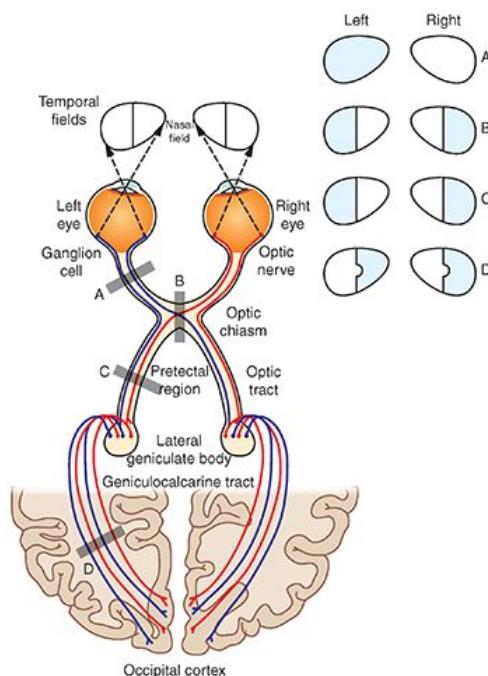


FIGURE 3.17 Visual impulses from the retina pass to the optic chiasm, where fibers from the nasal halves of the retina cross to the opposite side to join temporal fibers and form the optic tract. These fibers synapse in the lateral geniculate body before passing to the visual (occipital) area of the cerebral cortex. Visual field defects reflect lesions at various sites (A-D) in the nerve pathways.

Field of Vision

The field of vision is the area seen by the eye at a given instant. The area seen to the nasal side is called the *nasal field of vision*, and the area seen to the lateral side is called the *temporal field of vision* (see [Figure 3.17](#)).⁷⁶ An important use of visual fields is localization of lesions in the visual neural pathway. For example, anterior pituitary tumors may compress the optic chiasm, causing blindness in both temporal fields of vision (called *bitemporal hemianopia*). Thrombosis of the posterior cerebral artery is a cause of infarction of the visual cortex.

Muscular Control of Eye Movements

The cerebral control system for directing the eyes toward the object to be viewed is as important as the cerebral system for interpretation of the visual signals. Movements of the eyes are controlled by three pairs of skeletal muscles designated as the (1) medial and lateral recti, (2) superior and inferior recti, and (3) superior and inferior obliques. The medial and lateral recti contract reciprocally to move the eyes from side to side, the superior and inferior recti move the eyes upward or downward, and rotation of the globe is accomplished by the superior and inferior obliques. Each of the three sets of eye muscles is reciprocally innervated by cranial nerves III, IV, and VI so that one muscle of the pair contracts while the other relaxes.

Simultaneous movement of both eyes in the same directions is called *conjugate movement of the eyes*. Occasionally, abnormalities occur in the control system for eye movements that cause continuous nystagmus. Nystagmus is likely to occur when one of the vestibular apparatuses is damaged or when deep nuclei in the cerebellum are damaged or under the influence of ketamine anesthesia.

Innervation of the Eye

The eyes are innervated by the sympathetic and parasympathetic nervous system. The preganglionic fibers of the parasympathetic nervous system arise in the Edinger-Westphal nucleus of cranial nerve III and then pass to the ciliary ganglion, which gives rise to nerve fibers that innervate the ciliary muscle and sphincter of the iris. Sympathetic nervous system fibers innervate the radial fibers of the iris as well as several extraocular structures. Stimulation of the parasympathetic nervous system fibers to the eye excites the ciliary sphincter, causing miosis. Conversely, stimulation of sympathetic nervous system fibers to the eye excites the radial fibers of the iris and causes mydriasis. Pupillary response to autonomic tone is generally unreliable under anesthesia as many drugs used in anesthesia cause different effects on pupillary function. For example, volatile anesthetics cause midrange pupillary dilation while opioids cause pupillary constriction. Monitoring of pupillary diameter provides some indication of the residual opioid activity on anesthetic emergence.

Horner Syndrome

Interruption of the superior cervical chain of the sympathetic nervous system innervation to the eye results in miosis, ptosis, and vasodilation with absence of sweating on the ipsilateral side of the body, commonly referred to as *Horner syndrome*. Miosis occurs because of interruption of sympathetic nervous system innervation to the radial fibers of the iris. Ptosis reflects the normal innervation of the superior palpebral muscle by the sympathetic nervous system. Horner syndrome often occurs following stellate ganglion block and is occasionally a complication of interscalene block of the brachial plexus.

Hearing

Receptors for hearing and equilibrium are housed in the inner ear ([Figure 3.18](#)).⁷⁶ The external ear focuses sound waves on the ear drum, which oscillates in contact with the bones of the middle ear. The sound is amplified at the oval window, where the vibrations are transmitted to the hair cells of the cochlea in the inner

ear. The anatomic arrangement of the hair cells results in their responding to different frequencies, performing a mechanical Fourier transformation of the incoming sound waves. The electrical current generated from activation of a hair cell travels from the auditory nerve to the inferior colliculus and auditory cortex.

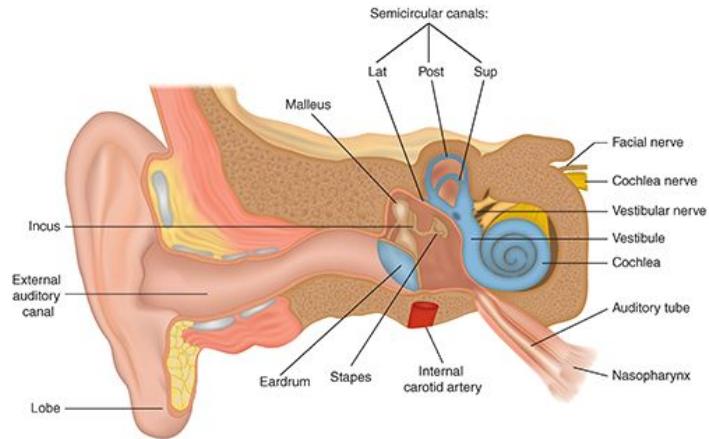


FIGURE 3.18 Schematic diagram of the outer and inner ear. Abbreviations: Lat, lateral; Post, posterior; Sup, superior.

The Eustachian tube connects the middle ear with the posterior tonsillar pillars and allows pressures on both sides of the tympanic membrane to be equalized during chewing or swallowing. Chronic obstruction of the Eustachian tube is often treated by placing small tubes through the eardrum, which is one of the most common procedures in children.⁸⁰ Nitrous oxide may increase middle ear pressure and has been associated with rupture of the tympanic membrane when the Eustachian tube is obstructed.⁸¹

Perioperative Hearing Impairment

Perioperative hearing impairment is often subclinical and may go unnoticed unless audiology is performed.⁸² Hearing loss (incidence may be as high as 50%) after dural puncture in the low-frequency range is most likely due to CSF leak and should resolve completely within days. Hearing loss following cardiopulmonary bypass, particularly in children, may be permanent and probably due to embolism and subsequent ischemic injury to areas of the organ of Corti.⁸³

Taste

Taste is mainly a function of taste buds located principally in the papillae of the tongue. Sweet, sour, salty, and bitter are the four primary sensations of taste. Sour taste is caused by acids. Sour taste intensity is approximately proportional to the logarithm of the hydrogen ion concentration (ie, pH). Sweet and salt are pleasurable tastes, of course. Bitter tastes are generally unpleasant. The bitter taste of alkaloids causes the individual to reject these substances. This may be protective as many plant toxins are alkaloids.

Smell

Olfactory receptors are located high in the nasal cavity. Each olfactory receptor is located on a single cilium. Olfactory receptors are coupled to G proteins, the activation of which increases activity of adenylyl cyclase, increasing the concentration of cAMP. A substance must be volatile and lipid soluble to stimulate olfactory cells. The importance of upward air movement in smell acuity is the reason sniffing improves the sense of smell, whereas holding one's breath prevents the sensation of unpleasant odors. Olfactory receptors adapt extremely rapidly, such that smell sensation may become extinct in about 60 seconds. Loss of the sense of taste and smell are unusual side effects of anesthesia. The effects 1 to 2 weeks likely related to the recovery of the peripheral receptors.⁸⁴

Nausea and Vomiting

Nausea is the conscious recognition of excitation of an area in the medulla that is associated with the vomiting (emetic) center ([Figure 3.19](#)).⁸⁵ Impulses are transmitted by afferent fibers of the parasympathetic and sympathetic nervous system to the vomiting center. Motor impulses transmitted via cranial nerves V, VII, IX, X, and XII to the gastrointestinal tract and through the spinal nerves to the diaphragm and abdominal muscles are required to cause the mechanical act of vomiting.

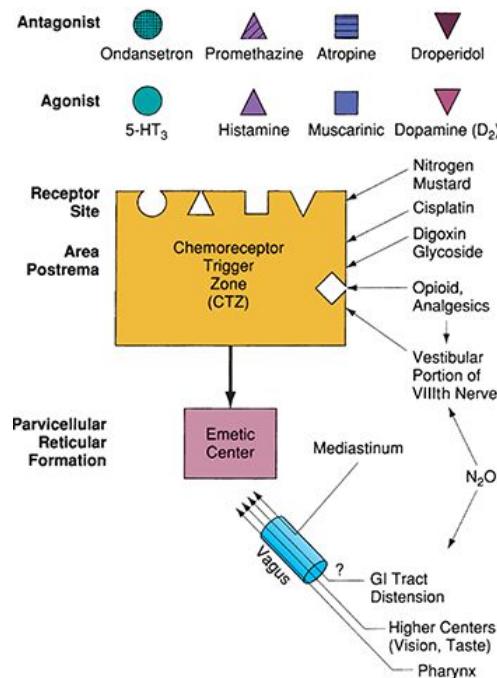


FIGURE 3.19 The chemoreceptor trigger zone and emetic center respond to a variety of stimuli resulting in nausea and vomiting. Abbreviations: 5-HT₃, 5-hydroxytryptamine; GI, gastrointestinal; N₂O, nitrous oxide.

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The medullary vomiting center is located close to the fourth cerebral ventricle and receives afferents from the (1) chemoreceptor trigger zone, (2) cerebral cortex, (3) labyrinthovestibular center, and (4) neurovegetative system. Impulses from these afferents lead to nausea and vomiting. The chemoreceptor trigger zone includes receptors for serotonin, dopamine, histamine, and opioids. Stimulation of the chemoreceptor trigger zone located on the floor of the fourth cerebral ventricle initiates vomiting independent of the vomiting center. The chemoreceptor trigger zone is not protected by the blood-brain barrier, and thus, this zone can be activated by chemical stimuli received through the systemic circulation as well as the CSF. The cerebral cortex stimulates vomiting through a response to certain smells and physiologic stresses. Motion can stimulate equilibrium receptors in the inner ear, which may also stimulate the medullary vomiting center. Blocking of impulses from the chemoreceptor trigger zone does not prevent vomiting due to irritative stimuli (ipecac) arising in the gastrointestinal tract.²¹ Multiple drugs that take advantage of this physiology have been developed to treat nausea and vomiting in general and under anesthesia in particular. As a general rule, drugs that act via different mechanisms and pathways are at least additive if not synergistic. This is true for the common antiemetic drugs used in anesthesiology.^{86,87}

Peripheral Nervous System

The peripheral nervous system is composed of the sensory and motor nerves that connect the CNS to the tissues and organs ([Figure 3.20](#)). These nerves are familiar to anesthesiologists as the targets for regional

anesthetic techniques, and the anatomy is well reviewed in many atlases of regional anesthesia.

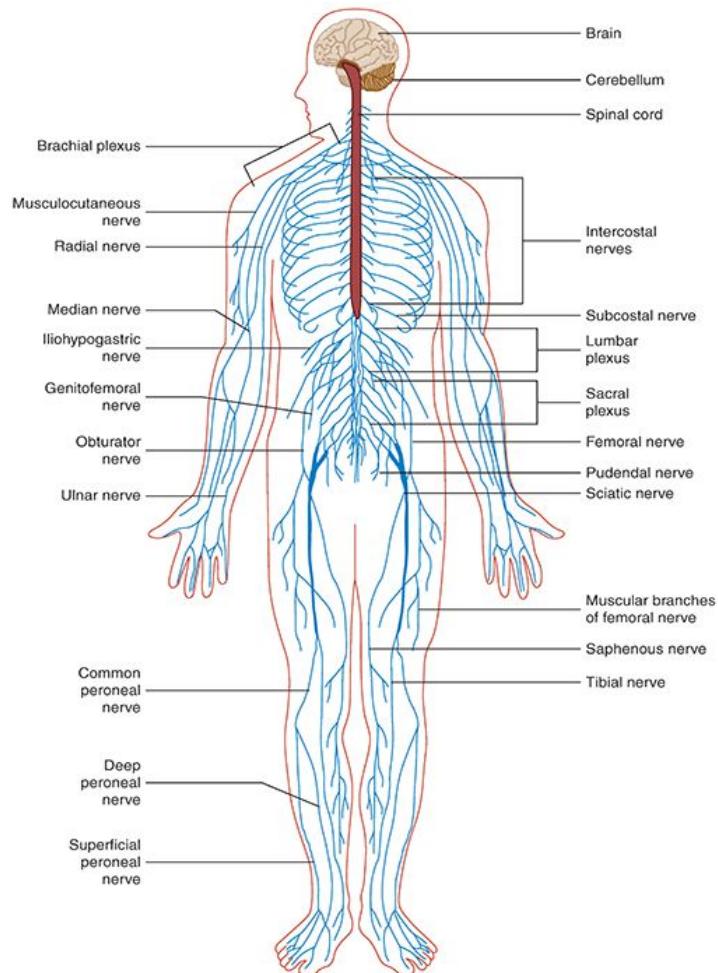


FIGURE 3.20 The peripheral nervous system connects the body tissues to the spinal cord and central nervous system.

Pathways for Peripheral Sensory Impulses

The peripheral nerves extend from the dendrite in the periphery to the dorsal root ganglion, where the cell body is located, and from there to the spinal cord by way of the dorsal root ([Figure 3.21](#)). By definition, dendrites conduct impulses toward the cell body, while axons conduct impulses away from the cell body. Thus, the portion of the nerve from the cell body to the peripheral receptor is a dendrite, while the relatively shorter connection from the dorsal root ganglion to the spinal cord is the axon. However, structurally the dendrite and the axon are indistinguishable, and the nerve behaves like one long axon, giving rise to the term *pseudounipolar neuron* that occasionally is used to describe peripheral nerves.

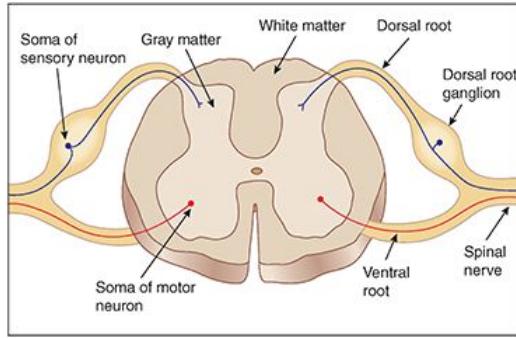


FIGURE 3.21 Cross-section of the spinal cord, showing the dorsal (posterior) and ventral (anterior) roots. The cell body of peripheral sensory nerves is in the dorsal root ganglion. The cell body of motor nerves is in the anterior horn.

After entering the spinal cord, peripheral sensory neurons synapse in the dorsal horn and give rise to long, ascending fiber tracts that transmit sensory information to the brain. These sensory signals are transmitted to the brain by the dorsal-lemniscal system, which includes dorsal column pathways and spinocervical tracts, and by anterolateral spinothalamic tracts (Figure 3.22).⁴ Impulses in the dorsal column pathways cross in the spinal cord to the opposite side before passing upward to the thalamus. Synapses in the thalamus are received by neurons that project into the somatic sensory area of the cerebral cortex. Nerve fibers of the anterolateral spinothalamic system cross in the anterior commissure to the opposite side of the spinal cord, where they turn upward toward the brain as the ventral (touch and pressure) and lateral (pain and temperature) spinothalamic tracts.

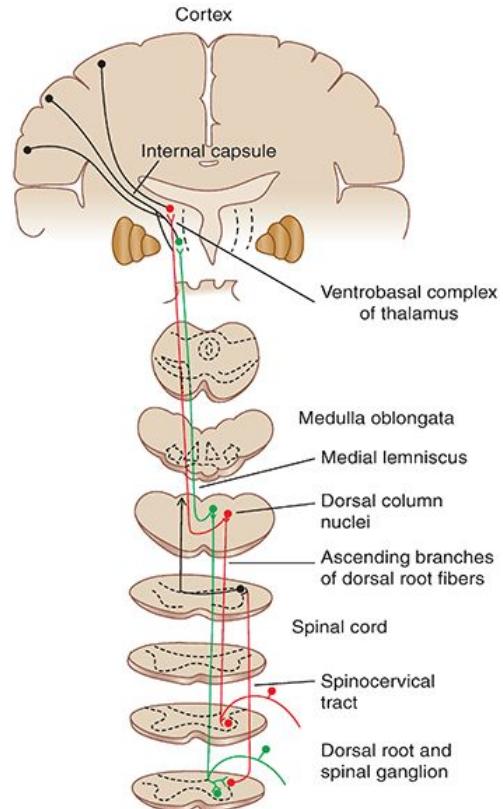


FIGURE 3.22 Sensory signals are transmitted to the brain by the dorsal column pathways and spinocervical tracts of the dorsal-lemniscal system.

Pathways for Peripheral Motor Responses

Sensory information is integrated at all levels of the nervous system and causes appropriate motor responses, beginning in the spinal cord with relatively simple reflex responses. Motor responses originating in the brainstem are more complex, whereas the most complicated and precise motor responses originate from the cerebral cortex.

Anterior motor neurons in the anterior horns of the spinal cord gray matter give rise to A- α fibers that leave the spinal cord by way of anterior nerve roots and innervate skeletal muscles. Skeletal muscles and tendons contain muscle spindles and Golgi tendon organs that operate at a subconscious level to relay information to the spinal cord and brain relative to changes in length and tension of skeletal muscle fibers. The stretch reflex is a reflex contraction of the skeletal muscle whenever stretch of the opposite balanced muscle results in stimulation of the muscle spindle. Tapping the patellar tendon elicits a knee jerk, which is a stretch reflex of the quadriceps femoris muscle. The ankle jerk is due to reflex contraction of the gastrocnemius muscle. Transmission of large numbers of facilitatory impulses from upper regions of the CNS to the spinal cord results in exaggerated stretch reflex responses. For example, lesions in the contralateral motor areas of the cerebral cortex, as caused by a cerebral vascular accident or brain tumor, cause greatly enhanced stretch reflexes. Clonus occurs when evoked muscle jerks oscillate. This phenomenon typically occurs when the stretch reflex is sensitized by facilitatory impulses from the brain, resulting in exaggerated facilitation of the spinal cord. When associated with recovery from general anesthesia, clonus as initiated by abrupt dorsiflexion of the foot can be eliminated by flexing the knees and keeping them in a flexed position.⁸⁸

Transection of the brainstem at the level of the pons (isolates the spinal cord from the rest of the brain) results in spasticity known as *decerebrate rigidity*. Decerebrate rigidity reflects diffuse facilitation of stretch reflexes.

The motor system is often divided into upper and lower motor neurons. Lower motor neurons originate in the spinal cord and directly innervate skeletal muscles. A lower motor neuron lesion is associated with flaccid paralysis, atrophy of skeletal muscles, and absence of stretch reflex responses. Upper motor neurons originate in the cerebral cortex or brainstem, and traverse down the anterior and lateral corticospinal paths until they connect with the lower motor neuron in the ventral horn of the spinal cord. Spastic paralysis with accentuated stretch reflexes is due to destruction of upper motor neurons in the brain.

Withdrawal flexor reflexes are a lower motor neuron reflex, typically elicited by a painful stimulus. Associated with withdrawal of the stimulated limb is extension of the opposite limb (cross-extensor reflex) that occurs 0.2 to 0.5 seconds later and serves to push the body away from the object causing the painful stimulus. The delayed onset of the cross-extensor reflex is due to the time necessary for the signal to pass through the additional neurons to reach the opposite side of the spinal cord.

Autonomic Nervous System

The autonomic nervous system controls the visceral functions of the body. In addition, the autonomic nervous system modulates systemic blood pressure, gastrointestinal motility and secretion, urinary bladder emptying, sweating, and body temperature maintenance. Activation of the autonomic nervous system occurs principally via centers located in the hypothalamus, brainstem, and spinal cord. The ANS is divided into the sympathetic, parasympathetic, and enteric nervous systems.

The sympathetic and the parasympathetic nervous systems usually function as physiologic antagonists such that the compiled action on any organ represents a balance of the influence of each component ([Table 3.4](#)). The sympathetic nervous system functions as an amplification response whereas the parasympathetic nervous system evokes discrete and narrowly targeted responses.

TABLE 3.4

Responses evoked by autonomic nervous system stimulation

	Sympathetic nervous system stimulation	Parasympathetic nervous system stimulation
Heart Sinoatrial node	Increase heart rate	Decrease heart rate

Atrioventricular node His-Purkinje system Ventricles	Increase conduction velocity Increase automaticity, conduction velocity Increase contractility, conduction velocity Automaticity	Decrease conduction velocity Minimal effect Minimal effects, slight decrease in contractility
Bronchial smooth muscle	Relaxation	Contraction
Gastrointestinal tract Motility Secretion Sphincters	Decrease Decrease Contraction	Increase Increase Relaxation
Gallbladder	Relaxation	Contraction
Urinary bladder Smooth muscle Sphincter	Relaxation Contraction	Contraction Relaxation
Uterus	Contraction	Variable
Ureter	Contraction	Relaxation
Eye Radial muscle Sphincter muscle Ciliary muscle	Mydriasis Relaxation for far vision	Miosis Contraction for near vision
Liver	Glycogenolysis Gluconeogenesis	Glycogen synthesis
Pancreatic beta cell secretion	Decrease	
Salivary gland secretion	Increase	Marked increase
Sweat glands	Increase ^a	Increase
Apocrine glands	Increase	
Arterioles Coronary Skin and mucosa Skeletal muscle Pulmonary	Constriction (α) Relaxation (β) Constriction Constriction (α) Relaxation (β) Constriction	Relaxation Relaxation Relaxation Relaxation

^aPostganglionic sympathetic fibers to sweat glands are cholinergic.

The enteric nervous system is arranged nontopographically, and its neurons and cells are located in the walls of the gastrointestinal tract. Although the gastrointestinal tract is influenced by sympathetic and parasympathetic nervous system activity, it is the enteric nervous system through the myenteric and submucous plexi that regulates digestive activity even in the presence of spinal cord transection.

An understanding of the anatomy and physiology of the autonomic nervous system is required for predicting the pharmacologic effects of drugs that act on either the sympathetic or parasympathetic nervous systems ([Table 3.5](#)). Relatively little is known about modulation of the enteric nervous system.

TABLE 3.5

Mechanism of action of drugs that act on the autonomic nervous system

Mechanism	Site	Drug
Inhibition of neurotransmitter synthesis	Central SNS	α -Methyldopa

False neurotransmitter	Central SNS	α -Methyldopa
Inhibition of uptake of neurotransmitter	Central noradrenergic synapses	Tricyclic antidepressants, cocaine
Displacement of neurotransmitter from storage sites	Central SNS PNS	Amphetamine Carbachol
Prevention of neurotransmitter release	SNS PNS	Bretylium Botulinum toxin
Mimic action of neurotransmitter at receptor	SNS α_1 α_2 β_1 β_2	Phenylephrine, methoxamine Clonidine dexmedetomidine Dobutamine Terbutaline, albuterol
Inhibition of action of neurotransmitter on postsynaptic receptor	SNS α_1 α_2 α_1 and α_2 β_1 β_1 and β_2 PNS M_1 M_1, M_2 N_1 N_2	Prazosin Yohimbine Phentolamine Metoprolol, esmolol Propranolol Pirenzepine Atropine Hexamethonium <i>d</i> -Tubocurarine
Inhibition of metabolism of neurotransmitter	SNS PNS	Monoamine oxidase inhibitors Neostigmine, pyridostigmine, edrophonium

Abbreviations: PNS, parasympathetic nervous system; SNS, sympathetic nervous system.

Anatomy of the Sympathetic Nervous System

Nerves of the sympathetic nervous system arise from the thoracolumbar (T1 to L2) segments of the spinal cord ([Figure 3.23](#)).⁴ These nerve fibers pass to the paravertebral sympathetic chains located lateral to the spinal cord. From the paravertebral chain, nerve fibers pass to tissues and organs innervated by the sympathetic nervous system.

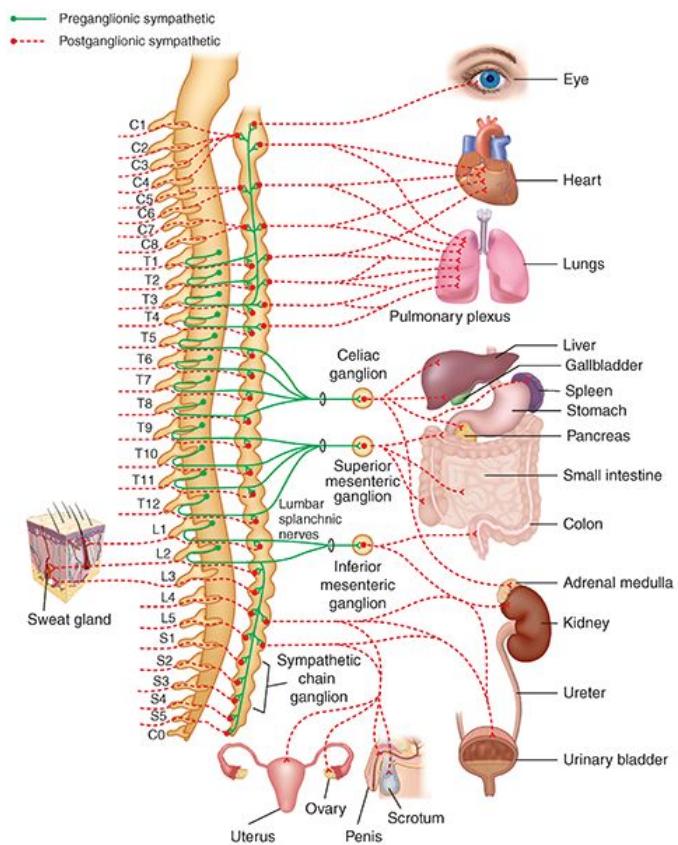


FIGURE 3.23 Anatomy of the sympathetic nervous system. Dashed lines represent postganglionic fibers in gray rami leading to spinal nerves for subsequent distribution to organs, blood vessels, and sweat glands.

Each nerve of the sympathetic nervous system consists of a preganglionic neuron and a postganglionic neuron ([Figure 3.24](#)). Cells bodies of preganglionic neurons are located in the intermediolateral horn of the spinal cord. Fibers from these preganglionic cell bodies leave the spinal cord with anterior (ventral) nerve roots and pass via white rami into 1 of 22 pairs of ganglia composing the paravertebral sympathetic chain. Axons of preganglionic neurons are mostly myelinated, slow-conducting type B fibers (see [Table 3.1](#)). In the ganglia of the paravertebral sympathetic chain, the preganglionic fibers can synapse with cell bodies of postganglionic neurons or pass cephalad or caudad to synapse with postganglionic neurons (mostly unmyelinated type C fibers) in other paravertebral ganglia. Postganglionic neurons then exit from paravertebral ganglia to travel to various peripheral organs. Other postganglionic neurons return to spinal nerves by way of gray rami and subsequently travel with these nerves to influence vascular smooth muscle tone and the activity of piloerector muscles and sweat glands.

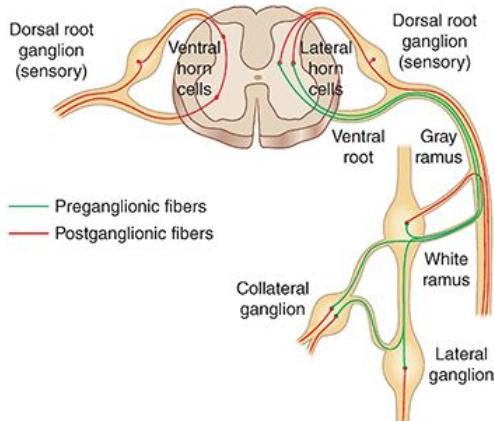


FIGURE 3.24 Anatomy of a sympathetic nervous system nerve. Preganglionic fibers pass through the white ramus to a paravertebral ganglion, where they may synapse, course up the sympathetic chain to synapse at another level, or exit the chain without synapsing to pass to an outlying collateral ganglion.

Fibers of the sympathetic nervous system are not necessarily distributed to the same part of the body as the spinal nerve fibers from the same segments. For example, fibers from T1 usually ascend in the paravertebral sympathetic chain into the head, T2 into the neck, T3 to T6 into the chest, T7 to T11 into the abdomen, and T12 and L1 to L2 into the legs. The distribution of these sympathetic nervous system fibers to each organ is determined in part by the position in the embryo from which the organ originates. In this regard, the heart receives many sympathetic nervous system fibers from the neck portion of the paravertebral sympathetic chain because the heart originates in the neck of the embryo. Abdominal organs receive their sympathetic nervous system innervation from the lower thoracic segments, reflecting the origin of the gastrointestinal tract from this area.

Anatomy of the Parasympathetic Nervous System

Nerves of the parasympathetic nervous system leave the CNS through cranial nerves III, V, VII, IX, and X (vagus) and from the sacral portions of the spinal cord ([Figure 3.25](#)).⁴ About 75% of all parasympathetic nervous system fibers are in the vagus nerves passing to the thoracic and abdominal regions of the body. As such, the vagus nerves supply parasympathetic innervation to the heart, lungs, esophagus, stomach, small intestine, liver, gallbladder, pancreas, and upper portions of the uterus. Fibers of the parasympathetic nervous system in cranial nerve III pass to the eye. The lacrimal, nasal, and submaxillary glands receive parasympathetic nervous system fibers via cranial nerve VII, whereas the parotid gland receives parasympathetic nervous system innervation via cranial nerve IX.

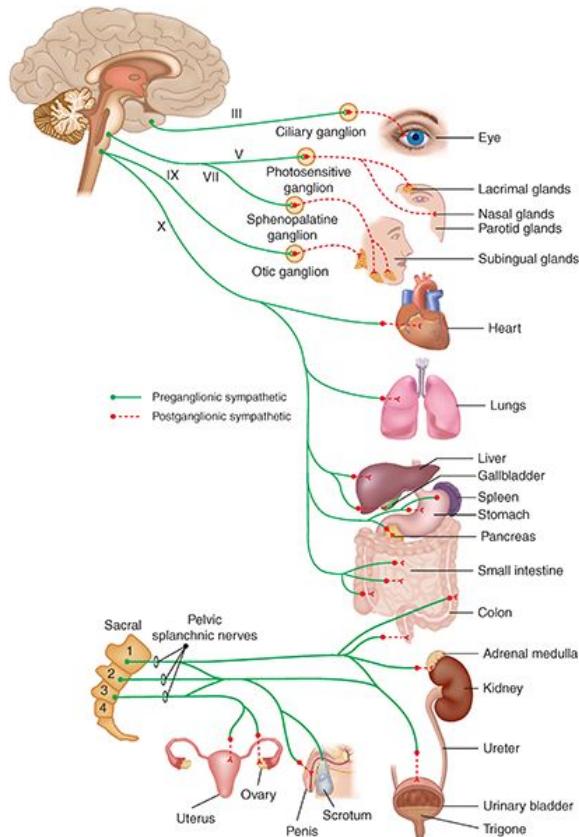


FIGURE 3.25 Anatomy of the parasympathetic nervous system.

The sacral part of the parasympathetic nervous system consists of the second and third sacral nerves, and, occasionally, the first and fourth sacral nerves. Sacral nerves form the sacral plexus on each side of the spinal cord. These nerves distribute fibers to the distal colon, rectum, bladder, and lower portions of the uterus. In addition, parasympathetic nervous system fibers to the external genitalia transmit impulses that elicit sexual responses.

In contrast to the sympathetic nervous system, preganglionic fibers of the parasympathetic nervous system pass uninterrupted to ganglia near or in the innervated organ (see [Figure 3.25](#)).⁴ Postganglionic neurons of the parasympathetic nervous system are short because of the location of the corresponding ganglia. This situation contrasts with the sympathetic nervous system, in which postganglionic neurons are relatively long, reflecting their origin in the ganglia of the paravertebral sympathetic chain, which is often distant from the innervated organ. Furthermore, unlike the amplified and diffuse discharges characteristic of sympathetic nervous system responses, activation of the parasympathetic nervous system is tonic and discrete. The vasodilatory effects of acetylcholine depend on the integrity of the vascular endothelium because activation of muscarinic receptors on the endothelium results in the release of nitric oxide.⁸⁹

Physiology of the Autonomic Nervous System

Preganglionic fibers of both the sympathetic and parasympathetic ganglia use acetylcholine as a transmitter activating nicotinic acetylcholine receptors with different subunit composition than those that mediate CNS function and muscle activation.⁹⁰ Postganglionic fibers of the sympathetic nervous system secrete norepinephrine as the neurotransmitter. These norepinephrine-secreting neurons are classified as *adrenergic fibers*. Postganglionic fibers of the parasympathetic nervous system secrete acetylcholine as the. These acetylcholine-secreting neurons are classified as *cholinergic fibers*. In addition, innervation of sweat glands and some blood vessels is by postganglionic sympathetic nervous system fibers that release acetylcholine as the neurotransmitter.

Norepinephrine as a Neurotransmitter

Synthesis

Norepinephrine acts as a neurotransmitter in the central and peripheral nervous systems. Synthesis of norepinephrine involves a series of enzyme-controlled steps that begin in the cytoplasm of postganglionic sympathetic nerve endings (varicosities) and are completed in the synaptic vesicles ([Figure 3.26](#)). For example, the initial enzyme-mediated steps leading to the formation of dopamine take place in the cytoplasm. Dopamine then enters the synaptic vesicle, where it is converted to norepinephrine by dopamine β -hydroxylase. The enzyme is present in noradrenergic cells of the locus coeruleus and postganglionic sympathetic fibers. Altered activity of the enzyme dopamine β -hydroxylase and therefore lower levels of norepinephrine has been reported in neurologic and psychiatric disorders including Alzheimer disease, posttraumatic stress disorder, and major depressive disorder.⁹¹ These enzymes are not highly specific, and other endogenous substances, as well as certain drugs, may be acted on by the same enzyme. For example, dopa-decarboxylase can convert the antihypertensive drug α -methyldopa to α -methyldopamine, which is subsequently converted by dopamine β -hydroxylase to the weakly active (false) neurotransmitter α -methylnorepinephrine that decreases the activation of central α_1 -adrenergic synapses and results in the reduction of blood pressure.

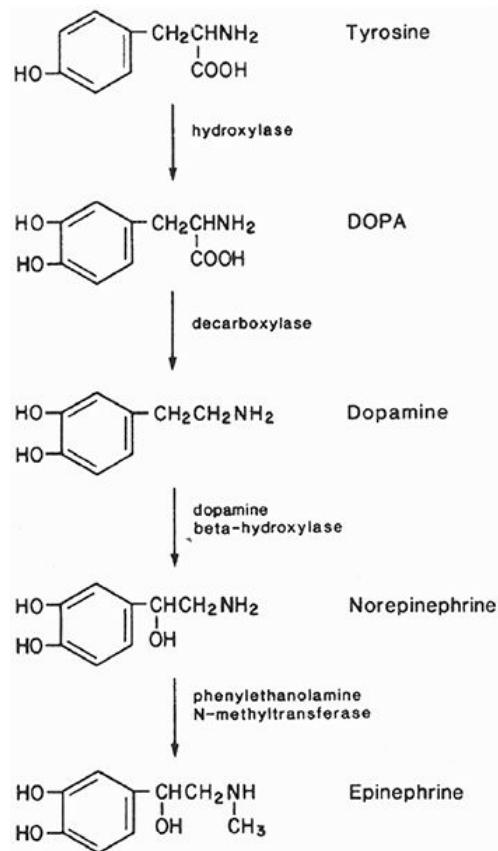


FIGURE 3.26 Steps in the enzymatic synthesis of endogenous catecholamines and neurotransmitters.

Storage and Release

Like most neurotransmitters, norepinephrine is stored in synaptic vesicles. In response to an action potential, it is released into the synaptic cleft where it interacts with pre- and postsynaptic receptors. Adrenergic fibers can sustain output of norepinephrine during prolonged periods of stimulation. Tachyphylaxis in response to

repeated administration of ephedrine and other indirect-acting sympathomimetics may reflect depletion of the norepinephrine stored in sympathetic nerve endings rather than an effect at the postsynaptic receptor.

Termination of Action

Termination of the action of norepinephrine is by (1) uptake (reuptake) back into postganglionic sympathetic nerve endings, (2) dilution by diffusion from receptors, and (3) metabolism by the enzymes monoamine oxidase (MAO) and catechol-*O*-methyltransferase (COMT). Norepinephrine released in response to an action potential exerts its effects at receptors for only a brief period, reflecting the efficiency of these termination mechanisms.

Reuptake

Uptake of previously released norepinephrine back into postganglionic sympathetic nerve endings is probably the most important mechanism for terminating the action of this neurotransmitter on receptors. As much as 80% of released norepinephrine undergoes reuptake. Reuptake provides a source for reuse of norepinephrine in addition to synthesis.

It is likely that two active transport systems are involved in reuptake of norepinephrine, with one system responsible for uptake into the cytoplasm of the varicosity and a second system for passage of norepinephrine into the synaptic vesicle for storage and reuse. The active transport system for norepinephrine uptake can concentrate the neurotransmitter 10,000-fold in postganglionic sympathetic nerve endings. Magnesium and adenosine triphosphate are essential for function of the transport system necessary for the transfer of norepinephrine from the cytoplasm into the synaptic vesicle. The transport system for uptake of norepinephrine into cytoplasm is blocked by numerous drugs, including cocaine and tricyclic antidepressants.

Metabolism

Metabolism of norepinephrine is of relatively minor significance in terminating the actions of endogenously released norepinephrine. The exception may be at some blood vessels, where enzymatic breakdown and diffusion account for the termination of action of norepinephrine. Norepinephrine that undergoes uptake is vulnerable to metabolism in the cytoplasm of the varicosity by MAO. Any neurotransmitter that escapes reuptake is vulnerable to metabolism by COMT, principally in the liver. Inhibitors of MAO including some antidepressants cause an increase in tissue levels of norepinephrine and may be accompanied by a variety of pharmacologic effects. Conversely, no striking pharmacologic change accompanies inhibition of COMT.

The primary urinary metabolite resulting from metabolism of norepinephrine by MAO or COMT is 3-methoxy-4-hydroxymandelic acid. This metabolite is also referred to as *vanillylmandelic acid (VMA)*. Normally, the 24-hour urinary excretion of 3-methoxy-4-hydroxymandelic acid is 2 to 4 mg, representing primarily norepinephrine that is deaminated by MAO in the cytoplasm of the varicosity of the postganglionic sympathetic nerve endings. Elevated levels of urinary vanillylmandelic acid suggests excessive circulating norepinephrine as in pheochromocytoma or a drug induced reduction in metabolism.

Acetylcholine as a Neurotransmitter

Synthesis

Acetylcholine is synthesized in the cytoplasm of varicosities of the preganglionic and postganglionic parasympathetic nerve endings. The enzyme choline acetyltransferase is responsible for catalyzing the combination of choline with acetyl coenzyme A to form acetylcholine. Choline enters parasympathetic nerve endings from the extracellular fluid through an active transport system. Acetyl coenzyme A is synthesized in mitochondria present in high concentrations in parasympathetic nerve endings.

Storage and Release

Acetylcholine is stored in synaptic vesicles for release in response to an action potential. Arrival of an action potential at a parasympathetic nerve ending results in the release of 100 or more vesicles of acetylcholine. It is estimated that a single nerve ending contains >300,000 presynaptic vesicles of acetylcholine.

Metabolism

Acetylcholine has a brief effect at receptors (<1 millisecond) because of its rapid hydrolysis by acetylcholinesterase to choline and acetate. Choline is transported back into parasympathetic nerve endings, where it is used for synthesis of new acetylcholine. Plasma cholinesterase is an enzyme found in low concentrations around acetylcholine receptors, being present in the highest amounts in plasma. The physiologic significance of plasma cholinesterase is unknown, as it is too slow to be physiologically important in the metabolism of acetylcholine. Absence of plasma cholinesterase produces no detectable clinical signs or symptoms until a drug such as succinylcholine or mivacurium is administered that require it for metabolism.

Residual Autonomic Nervous System Tone

The sympathetic and parasympathetic nervous systems are continually active, and this basal rate of activity is referred to as *sympathetic* or *parasympathetic tone*. The value of this tone is that it permits alterations in sympathetic or parasympathetic nervous system activity to mediate a fine increase or decrease in responses at innervated organs. For example, sympathetic nervous system tone normally keeps blood vessels about 50% constricted. As a result, increased or decreased sympathetic nervous system activity produces corresponding changes in systemic vascular resistance. If sympathetic tone did not exist, the sympathetic nervous system could only cause vasoconstriction.

In addition to continual direct activity of the sympathetic nervous system, a portion of overall sympathetic tone reflects basal secretion of norepinephrine and epinephrine by the adrenal medulla. The normal resting rate of secretion of norepinephrine is about 0.05 µg/kg/minute, and epinephrine is about 0.2 µg/kg/minute. These secretion rates are nearly sufficient to maintain systemic blood pressure in a normal range even if all direct sympathetic nervous system innervation to the cardiovascular system is removed.

Determination of Autonomic Nervous System Function

Autonomic dysfunction is associated with aging and diabetes mellitus. As anesthesia alters autonomic function, the combination of anesthesia and existing autonomic neuropathy can result in hemodynamic instability and cardiac complications. This may increase operative risk and can be associated with increased morbidity and mortality.⁹² Diagnosis of autonomic neuropathy in patients with diabetes mellitus is facilitated by tests of cardiovascular function (**Table 3.6**). Autonomic neuropathy is best assessed using heart rate variability or the difference between R wave intervals in an electrocardiogram. These tests measure activity of the sympathetic and parasympathetic nervous systems and precede changes in the measures of blood pressure. Simply stated, increased variability indicates a balance where parasympathetic tone is predominant and decreased variability is found in sympathetic excess and in autonomic neuropathy such as in diabetes. In addition to clinical tests of autonomic function, sensitive techniques for measuring plasma catecholamines are available. Interpretation of these data is confounded by other influences. Plasma epinephrine concentrations (normally 100-400 pg/mL) reflect adrenal release but vary greatly with psychological and physical stress. Plasma norepinephrine concentrations (normally 100-400 pg/mL) reflect both sympathetic nervous system and adrenal activity. Unlike plasma epinephrine levels, plasma norepinephrine concentrations reflect spillover from neuroeffector junctions, which may represent 10% to 20% of total release and vary among various organ systems. Because of these limitations, plasma catecholamine levels are not routinely measured for clinical diagnosis. On the other hand, as previously mentioned, 24-hour measurement urine catecholamines and metabolites avoids error due to moment to moment variability, providing an “area under the curve” that is useful in the diagnosis of hypersympathetic states such as pheochromocytoma.

TABLE 3.6

Clinical assessment of autonomic nervous system function

Clinical observation	Method of measurement	Normal value
Parasympathetic nervous system		
Heart rate	Patient blows into a mouthpiece maintaining a pressure of 40 mm Hg for	Ratio >1.21

response to Valsalva	15 seconds. The Valsalva ratio is the ratio of the longest R-R interval on the electrocardiogram immediately after release to the shortest R-R interval during the maneuver.	
Heart rate response to standing	Heart rate is measured as the patient changes from the supine to standing position (increase maximal around 15th beat after standing and slowing maximal around 30th beat). The response to standing is expressed as the “30:15” ratio and is the ratio of the longest R-R interval (around 30th beat) to the shortest R-R interval (around 15th beat).	Ratio >1.04
Heart response to deep breathing	Patient takes six deep breaths in 1 minute. The maximum and minimum heart rates during each cycle are measured, and the mean of the differences (maximum heart rate–minimum heart rate) during three successive breathing cycles is taken as the maximum–minimum heart rate.	Mean difference >15 beats per minute
Sympathetic nervous system		
Blood pressure response to standing	The patient changes from the supine to standing position, and the standing systolic blood pressure is subtracted from the supine systolic blood pressure.	Difference <10 mm Hg
Blood pressure response to sustained handgrip	The patient maintains a handgrip of 30% of maximum squeeze for up to 5 minutes. The blood pressure is measured every minute, and the initial diastolic blood pressure is subtracted from the diastolic blood pressure just prior to release.	Difference >16 mm Hg

Aging and Autonomic Nervous System Dysfunction

Common clinical manifestations of autonomic nervous system dysfunction in elderly patients are orthostatic hypotension, postprandial hypotension, hypothermia, and heat stroke. These responses reflect limited ability of elderly patients to adapt to stresses with vasoconstriction and vasodilation as mediated by the autonomic nervous system. Decreased autonomic nervous system function in elderly patients is due to fewer preganglionic terminals and therefore decreased response to catecholamines. Plasma epinephrine concentrations and the numbers of β -adrenergic receptors are unchanged with aging. Plasma norepinephrine concentrations increase with age, suggesting a primary physiologic deficit in reuptake mechanisms.⁹³

Clinically, there is attenuation of physiologic responses to β -adrenergic stimulation in the elderly. Exogenous β -adrenergic agonists have less profound effects on heart rate.⁹⁴ This decreased response to adrenergic stimulation seems to reflect decreased affinity (number of receptors unchanged) of β receptors for the neurotransmitter and decreases in coupling of stimulatory G proteins and adenylate cyclase units.

Diabetic Autonomic Neuropathy

Diabetic autonomic neuropathy is present in 20% to 40% of insulin-dependent diabetic patients. Common manifestations of diabetic autonomic neuropathy include impotence, diarrhea, postural hypotension, sweating abnormalities, and gastroparesis. When impotence or diarrhea is the sole manifestations of autonomic neuropathy, there is little impact on survival. Conversely, 5-year mortality rates may exceed 50% when postural hypotension or gastroparesis is present. Anesthetic risk is increased in diabetic patients with autonomic neuropathy associated with gastroparesis (aspiration hazard) and postural hypotension (hemodynamic instability) and is a marker for vasculopathy in other organs including the heart.⁹⁵

Chronic Sympathetic Nervous System Stimulation

Chronic sympathetic nervous system stimulation may increase morbidity and mortality. Pheochromocytoma is characterized by explosive release of catecholamines. Patients with pheochromocytoma often present with

severe episodic hypertension and tachycardia. Even physiologic responses and surgical stress that lead to sustained autonomic nervous system hyperactivity can result in metabolic and endocrine responses including increased glucose levels from gluconeogenesis. Preoperative alpha and beta blockade has been used in the past aimed at decreasing morbidity and mortality from pheochromocytoma resection. Historically, alpha blockade was established prior to initiating beta blockade. Beta blockade alone can result in unopposed alpha stimulation from circulating catecholamines. The unopposed alpha stimulation can cause vasoconstriction and worsening of blood pressure. Conflicting studies looking at alpha and beta blockade have not brought into question the necessity of this preoperative medical treatment. The use of alpha blockade has not shown to significantly reduce hemodynamic lability and yet mortality remains low.^{96,97}

Acute Denervation

Acute removal of sympathetic nervous system tone, as produced by a regional anesthetic or spinal cord transection, results in immediate maximal vasodilation of blood vessels (spinal shock). In the anesthetic setting this is transient and can be treated with fluid or alpha vasoconstrictors. In the chronic setting, over several days, intrinsic tone of vascular smooth muscle increases, usually restoring almost normal vasoconstriction.

Denervation Hypersensitivity

Denervation hypersensitivity is the increased responsiveness (decreased threshold) of the innervated organ to norepinephrine or epinephrine that develops during the first week or so after acute interruption of autonomic nervous system innervation. The presumed mechanism for denervation hypersensitivity is the proliferation of receptors (upregulation) on postsynaptic membranes that occurs when norepinephrine or acetylcholine is no longer released at synapses. As a result, more receptor sites become available to produce an exaggerated response when circulating neurotransmitter does become available.

Adrenal Medulla

The adrenal medulla is innervated by preganglionic fibers that bypass the sympathetic chain. As a result, these fibers pass directly from the spinal cord to the adrenal medulla. Cells of the adrenal medulla are derived embryologically from neural tissue and are analogous to postganglionic sympathetic neurons. Stimulation of the sympathetic nervous system causes release of epinephrine (80%) and norepinephrine from the adrenal medulla. As such, epinephrine and norepinephrine released by the adrenal medulla into the blood function as hormones and not as neurotransmitters.

Synthesis

In the adrenal medulla, most of the synthesized norepinephrine is converted to epinephrine by the action of phenylethanolamine-N-methyltransferase (see [Figure 3.26](#)). Activity of this enzyme is enhanced by cortisol, which is carried by the intra-adrenal portal vascular system directly to the adrenal medulla. For this reason, any stress that releases glucocorticoids also results in increased synthesis and release of epinephrine.

Release

The triggering event in the release of epinephrine and norepinephrine from the adrenal medulla is the liberation of acetylcholine by preganglionic cholinergic fibers. Acetylcholine acts on α_3 and β_4 subunit containing nicotinic receptors in the adrenal medulla, resulting in a change in permeability (localized depolarization) that permits entry of calcium ions through extracellular calcium channels. Calcium ions result in extrusion, by exocytosis, of synaptic vesicles containing epinephrine.

Norepinephrine and epinephrine released from the adrenal medulla evoke responses similar to direct stimulation of the sympathetic nervous system. The difference, however, is that effects are greatly prolonged (10-30 seconds) compared with the brief duration of action on receptors that is produced by norepinephrine released as a neurotransmitter from postganglionic sympathetic nerve endings. The prolonged effect of circulating epinephrine and norepinephrine released by the adrenal medulla reflects the time necessary for metabolism of these substances by COMT and MAO.

Circulating norepinephrine from the adrenal medulla causes vasoconstriction of blood vessels, inhibition of the gastrointestinal tract, increased cardiac activity, and dilatation of the pupils (see [Table 3.4](#)). The effects of circulating epinephrine differ from those of norepinephrine in that the cardiac and metabolic effects of epinephrine are greater, whereas relaxation of blood vessels in skeletal muscles reflects a predominance of beta- over alpha-effects at low concentrations of epinephrine. Circulating norepinephrine and epinephrine released by the adrenal medulla and acting as hormones can substitute for sympathetic nervous system innervation of an organ. Another important role of the adrenal medulla is the ability of circulating norepinephrine and epinephrine to stimulate areas of the body that are not directly innervated by the sympathetic nervous system. For example, the metabolic rate of all cells can be influenced by hormones released from the adrenal medulla, even though these cells are not directly innervated by the sympathetic nervous system.

Thermoregulation

Body temperature is determined by the relationship between heat production and heat dissipation. Heat is continually being produced in the body as a product of metabolism. As heat is produced, it is also continuously being lost to the environment. Both heat generation and heat loss are adjusted in order to regulate body temperature within narrow limits. Normal core body temperatures range from about 36°C to 37.5°C and undergo circadian fluctuations, being lowest in the morning and highest in the evening.

Heat Loss

The important mechanisms of heat loss from the body include radiation, conduction, convection, and evaporation. Their relative contributions vary and depend upon the environmental circumstances.⁹⁸ The skin is the most important route for heat dissipation, while the lungs account for only about 10% of heat loss. Under typical circumstances, most heat (about 60%) is lost by radiation. A warm object emits energy in the form of radiation, predominantly in the infrared range, independent of ambient air temperature. Significant radiant losses can occur from the unclothed patient in the operating room. In infant incubators, radiant heat losses occur from the exposed infant. Radiant heat loss is countered by heating the surrounding surfaces so that radiant heat loss is offset by the absorption of radiant heat from nearby surfaces. Radiant heat loss is also countered by blankets, which absorb and then return radiant heat.

Conduction of heat from the body occurs by direct contact with a cooler object, for example, between the patient and cold air or an adjacent mattress. The area of the conducting surfaces, the temperature difference, and the heat capacity affects conductive heat transfer. Conductive loss to still air is limited because a stationary layer of air next to the skin acts as a good insulator. Air has a very low heat capacity and warms quickly, thus promptly eliminating the temperature gradient. In humans, piloerection reduces heat loss by trapping a layer of air next to the skin.

Although pure conduction accounts for <5% of heat loss, conductive heat loss to air is greatly facilitated by air movement and is termed *convection* or *facilitated conduction*. Thus, a fan is comfortable on a hot summer day because it facilitates heat loss. The rate of convective loss depends on both the air temperature and its velocity (the “wind-chill” phenomenon). Convection accounts for approximately 15% to 30% of heat loss in the operating room but increases significantly in high “wind-chill” environments such as a laminar flow unit. However, significant convective heat loss occurs even in a draft-free environment because warmed air rises to be replaced by denser cold air, thus maintaining cutaneous airflow.

Evaporative heat losses are important because significant energy is required to vaporize water. Evaporation from the skin accounts for about 20% of total heat loss. The magnitude of evaporative loss depends upon environmental humidity, exposed skin surface area, presence of diaphoresis, wound and bowel exposure, and application of fluid to the skin (prep solutions). Evaporation is the only mechanism by which the body can eliminate excess heat when the temperature of the surroundings is higher than that of the skin. Diaphoresis occurs in response to stimulation of the preoptic area of the hypothalamus. A normal individual has a maximal sweat production of about 700 mL per hour. With continued exposure to a warm environment, sweat production may increase to 1,500 mL per hour. Evaporation of this amount of sweat can remove heat from the body at a rate of >10 times the normal basal rate of heat production. Evaporation accounts for two-

thirds of the heat loss from the respiratory tract. Evaporative heat and fluid loss are important considerations during surgery in which large segments of moist bowel are exposed for evaporation. Reductions in core temperature also follow infusions of cold intravenous fluids and blood products.

Regulation of Body Temperature

Body temperature is regulated by feedback mechanisms predominantly mediated by the preoptic nucleus of the anterior hypothalamus,⁹⁹ which integrates afferent input from thermoreceptors in the skin, deep tissues, and spinal cord. Afferent thermoregulatory input is modulated in the brainstem and spinal cord before arrival in the hypothalamus. Heat-sensitive neurons in the preoptic nucleus receive additional thermal input from extrahypothalamic areas of the brain. Reflex responses to cold (vasoconstriction, piloerection, shivering, and nonshivering thermogenesis) originate in the posterior hypothalamus. Reflex responses to heat (vasodilatation, sweating) originate in the anterior hypothalamus.

The hypothalamic thermostat detects body temperature changes and initiates autonomic, somatic, and endocrine responses when the various set points are reached. However, in the awake individual, behavioral responses (putting on a jacket) usually occur before the core temperature reaches the set points. If the behavioral response to hypothermia fails or is abolished by anesthesia, the hypothalamic thermostat stimulates vasoconstriction at 36.5°C and shivering at 36.2°C. As a result, the rate of heat transfer to the skin is decreased, heat production rises from shivering, and body temperature increases.

There is a narrow range of normal core temperature, 36.7°C to 37.1°C, within which thermoregulatory responses are not triggered. General anesthesia abolishes much of the ability to regulate temperature through drug induced vasodilation and muscle relaxation. Maintenance of body temperature at a value close to the optimum for enzyme activity assures a constant rate of metabolism, optimal enzyme function, nervous system conduction, and skeletal muscle contraction. Even modest hypothermia (<36°C) reduces the drug metabolism, delaying emergence from anesthesia. Hyperthermia is even less well tolerated, as protein denaturation begins at about 42°C.

Nonshivering Thermogenesis

Nonshivering thermogenesis (alternatively called chemical thermogenesis) is an increase in the rate of cellular metabolism in brown adipose tissue evoked by sympathetic nervous system stimulation or by circulating catecholamines. In infants, chemical thermogenesis in brown fat located in the interscapular space and around the great vessels in the thorax and abdomen can increase the rate of heat production by as much as 200%. Historically, it was thought that adults had almost no brown fat; however, recent studies have shown functional brown adipose tissue in adults that becomes activated during exposure to cold.¹⁰⁰ In contrast to other fat depots, brown fat contains large numbers of mitochondria, and has extensive sympathetic innervation. Within these mitochondria, the generation of adenosine triphosphate is uncoupled as oxidative phosphorylation is short-circuited to generate heat. This process is dependent upon an uncoupling protein (UCP 1). Lipolysis and heat generation in brown fat is mediated via β-adrenergic receptors.

Shivering

Skeletal muscle activity is a major source of heat. Shivering increases body heat production in response to decreased core temperature. The posterior hypothalamic area responsible for the response to hypothermia controls reflex shivering. Shivering occurs due to both increased motor traffic via anterior motor neurons and to upregulation of the muscle stretch reflex. However, shivering is inefficient and induces significant metabolic demand. Awake patients find shivering intensely unpleasant.

Causes of Increased Body Temperature

A variety of disorders can increase body temperature. Those disorders resulting from thermoregulatory failure (excessive metabolic production of heat, excessive environmental heat, and impaired heat dissipation) are properly characterized as *hyperthermia*, whereas those resulting from intact homeostatic responses are categorized as *fever* (**Table 3.7**).⁹⁹

TABLE 3.7**Causes of hyperthermia**

Disorders associated with excessive heat production
Malignant hyperthermia
Neuroleptic malignant syndrome
Thyrotoxicosis
Delirium tremens
Pheochromocytoma
Salicylate intoxication
Drug abuse (cocaine, amphetamine, 3,4-methylenedioxymethamphetamine)
Status epilepticus
Exertional hyperthermia
Disorders associated with decreased heat loss
Autonomic nervous system dysfunction
Anticholinergics
Drug abuse (cocaine)
Dehydration
Occlusive dressings
Heat stroke
Disorders associated with dysfunction of the hypothalamus
Trauma
Tumors
Idiopathic hypothalamic dysfunction
Cerebrovascular accidents
Encephalitis
Neuroleptic malignant syndrome

In hyperthermic states, the hypothalamic set-point is normal, but peripheral mechanisms are unable to maintain body temperature that matches the set-point. In contrast, fever occurs when the hypothalamic set-point is increased by the action of circulating pyrogenic cytokines, causing intact peripheral mechanisms to conserve and generate heat until the body temperature increases to the elevated set-point. Despite their physiologic differences, hyperthermia and fever cannot be differentiated clinically based on the height of the temperature or its pattern. However, the clinical management of hyperthermia and fever are very different. The treatment of hyperthermia should be directed at promoting heat dissipation and terminating excessive heat production (eg, administration of dantrolene for malignant hyperthermia), whereas the treatment of fever should be directed at identification and eradication of pyrogens and lowering the thermoregulatory set-point with antipyretic drugs such as aspirin, acetaminophen, and cyclooxygenase inhibitors.

Fever

Pyrogens are bacterial and viral toxins that indirectly cause the set-point of the hypothalamic thermostat to increase. Bacterial pyrogens stimulate host inflammatory cells (mononuclear phagocytes) to generate endogenous pyrogens, including interleukins, prostaglandins, and tumor necrosis factor. Viruses do not release pyrogens directly but stimulate infected cells to release interferons α and β that act as endogenous pyrogens. All known endogenous pyrogens are polypeptides and are therefore unlikely to cross the blood–brain barrier. However, endogenous pyrogens have actions in the organum vasculosum of the lamina terminalis, which is a structure adjacent to the lateral ventricles that lies outside the blood–brain barrier. It is likely that endogenous pyrogens acting in the organum vasculosum of the lamina terminalis evoke the release of prostaglandins in the CNS, leading to stimulation of the preoptic nucleus and generation of the febrile response.⁷⁶

Chills

Sudden resetting of the hypothalamic thermostat to a higher level because of tissue destruction, pyrogens, or dehydration, results in a lag between blood temperature and the new hypothalamic set point. During this period, the person experiences chills and feels cold even though body temperature may be increased. The skin is cold because of cutaneous vasoconstriction. Chills continue until the body temperature increases to the new set point of the hypothalamic thermostat. As long as the process causing the hypothalamic thermostat to be set at a higher level is present, the body's core temperature will remain increased above normal. Sudden removal of the factor that is causing the body temperature to remain increased is accompanied by intense diaphoresis and feeling of warmth because of generalized cutaneous vasodilation.

Cutaneous Blood Flow

Cutaneous blood flow is a major determinant of heat loss. The cutaneous circulation is among the most variable in the body, reflecting its primary role in regulation of body temperature in response to alterations in the rate of metabolism and the temperature of the external surroundings. The skin's metabolic needs are so low that the typical cutaneous blood flow is about 10 times higher than needed to supply nutritive needs of the skin.

Cutaneous blood flow is largely regulated by the sympathetic nervous system. Vascular structures concerned with heat loss from skin consist of subcutaneous venous plexuses that can hold large quantities of blood. The cutaneous circulation of the fingers, palms, toes, and earlobes has richly innervated arteriovenous anastomoses that facilitate significant heat loss. In an adult, typical total cutaneous blood flow is about 400 mL per minute. This flow can decrease to as little as 50 mL per minute in severe cold and may increase to as much as 2,800 mL per minute in extreme heat. Patients with borderline cardiac function may become symptomatic in hot environments as the heart attempts to supply increased blood flow to the skin. During acute hemorrhage, the sympathetic nervous system can produce enough cutaneous vasoconstriction to transfer large amounts of blood into the central circulation. As such, the cutaneous veins act as an important blood reservoir that can supply 5% to 10% of the blood volume in times of need. Acute hemorrhage may be less well tolerated in a warm environment because the hypothalamic vasodilator response may override the vasoconstrictor response to hypovolemia. Inhaled anesthetics increase cutaneous blood flow, perhaps by inhibiting the temperature-regulating center of the hypothalamus.¹⁰¹

Perioperative Temperature Changes

The thermoregulatory system contains three key elements: afferent input, central processing, and the efferent response. General anesthesia affects all three elements and regional anesthesia affects both the afferent and efferent components. Thus, anesthesia and surgery in a cool environment makes perioperative hypothermia a likely occurrence (**Table 3.8**).^{102,103} General and regional anesthesia increase the homeostatic range to 4.0°C, approximately 20 times the normal range. The threshold for sweating and vasodilation is increased about 1°C, and the threshold for vasoconstriction and shivering is decreased about 3°C. As a result, anesthetized patients are relatively poikilothermic, with body temperatures determined by the environment. Anesthetics inhibit thermoregulation in a dose-dependent manner and inhibit vasoconstriction and shivering about 3 times as much as they restrict sweating.¹⁰⁴

TABLE 3.8
Events that contribute to decreases in body temperature during surgery
Resetting of the hypothalamic thermostat
Ambient temperature <21°C
Administration of unwarmed intravenous fluids
Drug-induced vasodilation
Basal metabolic rate decreased
Attenuated shivering response
Core compartment exposed to ambient temperature
Heat required to humidify inhaled dry gases

Alfentanil and propofol similarly lower the threshold for vasoconstriction and sweating. Volatile anesthetics such as isoflurane and desflurane decrease the threshold temperatures for cold responses in a nonlinear fashion. Nonshivering thermogenesis does not occur during general anesthesia in adults or infants.

Sequence of Temperature Changes During Anesthesia

In the awake individual, body heat is unevenly distributed. Tonic thermoregulatory vasoconstriction maintains a temperature gradient between the core and periphery of 2°C to 4°C. The core compartment that is insulated from the environment by the peripheral compartment, consists of the major viscera, and includes the head, chest, abdomen, and pelvis. Under general anesthesia, tonic vasoconstriction is attenuated and heat contained in the core compartment will move to the periphery, thus allowing the core temperature to decrease toward the anesthetic-induced lowered threshold for vasoconstriction. This core to peripheral heat redistribution is responsible for the 0.5°C to 1.55°C decrease in core temperature that occurs during the first hour of general anesthesia ([Figure 3.27](#)).¹⁰⁵ For this reason, protection from heat loss early in a surgical procedure is important to reduce the temperature gradient from the environment to the peripheral compartment as significant heat energy has been shunted to the periphery.

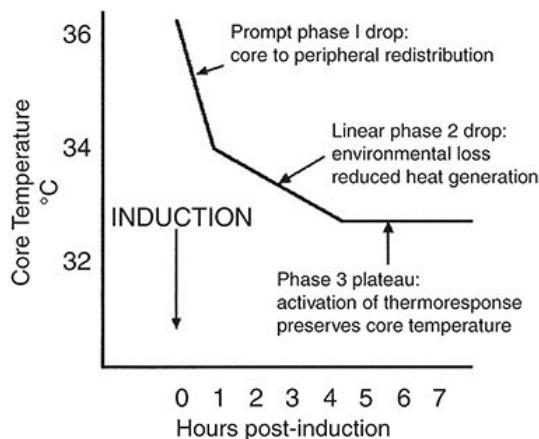


FIGURE 3.27 Graphic representation of the typical triphasic core temperature pattern that occurs after induction of anesthesia. Note that the phase 3 plateau may not occur, particularly during regional anesthesia or during combined regional and general anesthesia. Although core temperature is preserved during the phase 3 plateau, heat will continue to be lost to the environment from the peripheral compartment.

After the first hour of general anesthesia, the core temperature usually decreases at a slower rate. This decrease is nearly linear and occurs because continuing heat loss to the environment exceeds the metabolic production of heat. After 3 to 5 hours of anesthesia, the core temperature often stops decreasing (see [Figure 3.27](#)). This thermal plateau may reflect a steady state in which heat loss equals heat production. This type of thermal steady state is especially likely in patients who are well insulated or effectively warmed. However, if a patient becomes sufficiently hypothermic, activation of thermoregulatory vasoconstriction will occur, decreasing cutaneous heat loss and retaining heat in the core compartment. Intraoperative vasoconstriction thus reestablishes the normal core-to-periphery temperature gradient by preventing the loss of centrally generated metabolic heat to peripheral tissues. Although vasoconstriction may effectively maintain the core temperature plateau, mean body temperature and the total heat content of the body continue to decrease as continued loss of heat occurs from the peripheral compartment to the environment. Because reflex vasoconstriction is usually effective in maintaining core temperature, the intraoperative core temperature rarely decreases the additional 1°C necessary to trigger shivering during general anesthesia.¹⁰³

Although regional anesthesia is thought to have minimal effect upon the central processing and integration of the thermoregulatory response, afferent cold input from the lower body may be overridden by a sense of warmth from cutaneous vasodilatation. Decreases in core temperature of a similar or greater

magnitude to those experienced during general anesthesia may occur during spinal or epidural techniques despite the sensation of warmth. The initial redistributive temperature drop may be less precipitous during regional anesthesia because vasodilatation is restricted to the blocked area. However, because reflex vasoconstriction is abolished below the level of the block, the plateau phase seen during general anesthesia may not occur during regional anesthesia (see [Figure 3.27](#)). Indeed, core temperature may decrease sufficiently during regional anesthesia to trigger the shivering response. However, the ability of reflex shivering to generate heat is markedly attenuated because it is restricted to the unblocked upper body.

Beneficial Effects of Perioperative Hypothermia

Oxygen consumption is decreased by approximately 5% to 7% per °C of cooling. Even moderate decreases in core temperature of 1°C to 3°C below normal provide substantial protection against cerebral ischemia and arterial hypoxemia. Indeed, induced hypothermia to 28°C, as used during cardiopulmonary bypass, will reduce cerebral metabolic rate by 50%. Hypothetically, mild hypothermia (33°C-36°C) during operations likely to be associated with cerebral ischemia such as carotid endarterectomy and aneurysm clipping should be neuroprotective but there has not been conclusive evidence showing the benefit.[106,107](#) Operations involving aortic cross-clamping can jeopardize spinal cord perfusion and may also benefit from the increased margin of safety afforded by mild hypothermia. Mild hypothermia also slows the triggering of malignant hyperthermia.[108](#)

Outside the operating room, induced hypothermia after cardiac arrest from ventricular fibrillation has shown to improve survival and neurologic function.[109](#) More recent trials have shown that targeting a temperature of 36°C is as beneficial as 33°C.[110](#) It may be that actively controlling a temperature to avoid fever is what confers the neurologic benefit rather than the process of cooling. The main benefit of mild hypothermia accrues from a reduction in metabolic demand. Typical approaches to achieve mild hypothermia often include surface cooling. However, surface cooling may induce shivering, which will delay core cooling. For targeted temperature management after cardiac arrest, medications are often given to control shivering, including neuromuscular blockade.

Adverse Consequences of Perioperative Hypothermia

Perioperative hypothermia may predispose to several significant complications ([Table 3.9](#)). These include postoperative shivering (significantly increasing metabolic rate and cardiac work) and impaired coagulation (impaired platelet function, decreased activation of the coagulation cascade). Indeed, hypothermia-induced coagulopathy is associated with increased transfusion requirements. A 1°C decrease in temperature is associated with a 5% reduction in anesthetic requirements (MAC) and an increase in volatile anesthetic blood/gas solubility. Drug metabolism is decreased by hypothermia, particularly that of nondepolarizing neuromuscular-blocking drugs. These factors all conspire to delay emergence from anesthesia and delay recovery room discharge. Hypothermia also impairs wound healing and is associated with decreased resistance to surgical wound infection.[104](#) The underlying mechanism is thought to be hypothermia-induced vasoconstriction, which decreases wound perfusion and local tissue oxygen partial pressure. Perioperative hypothermia is also associated with delayed hospital discharge and an increased catabolic state. Shivering occurs in approximately 40% of unwarmed patients who are recovering from general anesthesia and is associated with substantial sympathetic nervous system activation and discomfort from the sensation of cold. Core hypothermia equal to a 1.5°C decrease triples the incidence of ventricular tachycardia and morbid cardiac events.[111](#)

TABLE 3.9

Immediate adverse consequences of perioperative hypothermia

Adverse outcome	Mechanism
Increased operative blood loss	Coagulopathy and platelet dysfunction Increased myocardial work load Increased sympathetic activity

Increased morbid cardiac events Dysrhythmias and myocardial ischemia Wound infection Delayed wound healing Delayed anesthetic emergence Delayed recovery room discharge	Sympathetic mediated cutaneous vasoconstriction Decreased drug metabolism and increased volatile agent solubility; decreased minimum anesthetic concentration Postanesthetic shivering; delayed recovery
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Perioperative Temperature Measurement

The significant adverse physiologic effects of changes in body temperature are a compelling reason to monitor body temperature during anesthesia. Unless hypothermia is specifically indicated, as for protection against tissue ischemia, it is recommended that intraoperative core temperature be maintained at $\geq 36^{\circ}\text{C}$. Measuring the temperature of the lower 25% of the esophagus (about 24 cm beyond the corniculate cartilages or site of the loudest heart sounds heard through an esophageal stethoscope) gives a reliable approximation of blood and cerebral temperature. Readings elsewhere in the esophagus are more likely to be influenced by the temperature of inhaled gases. A nasopharyngeal temperature probe positioned behind the soft palate gives a less reliable measure of cerebral temperature than a correctly positioned esophageal probe. Leakage of gases around the tracheal tube may also influence nasopharyngeal temperature measurements. Heat-producing bacteria in the gastrointestinal tract, cold blood returning from the lower limbs, and insulation of the probe by feces can all influence rectal temperature. Bladder temperature is also subject to a prolonged response time, particularly if urine flow is $<270 \text{ mL per hour}$.¹¹² Tympanic membrane and aural canal temperatures provide a rapidly responsive and accurate estimate of hypothalamic temperature and correlate well with esophageal temperature. Thermistors in pulmonary artery catheters provide the best continuous estimate of body temperature but are invasive. Skin temperature gives no information other than the temperature of that area of the skin.

Prevention of Perioperative Hypothermia

Passive or active airway heating and humidification contribute little to perioperative thermal management in adults because <10% of metabolic heat is lost via ventilation.¹⁰⁴ Each liter of intravenous fluid at ambient temperature that is infused into adult patients, or each unit of blood at 4°C decreases the mean core body temperature about 0.25°C . In this regard, the administration of unwarmed fluids can markedly decrease body temperature. Warming fluids to near 37°C is useful for preventing hypothermia, especially if large volumes of fluids are being infused.

The skin is the predominant source of heat loss during anesthesia and surgery, although evaporation from large surgical incisions may also be important. A high ambient temperature maintains normothermia in anesthetized patients, but temperatures of $>25^{\circ}\text{C}$ are uncomfortable for operating room personnel.

Covering the skin with surgical drapes or blankets can decrease cutaneous heat loss. A single layer of insulator decreases heat loss by approximately 30%, but additional layers do not proportionately increase the benefit.¹¹³ For this reason, active warming is needed to prevent intraoperative hypothermia. Forced-air warming is probably the most effective method available, although any method or combination of methods that maintains core body temperature near 36°C is acceptable.¹⁰⁴ Circulating warm water mattresses are generally ineffective because cutaneous blood flow to the back is limited in the supine position.

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Inhaled Anesthetics

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History

The discovery of the anesthetic properties of nitrous oxide, diethyl ether, and chloroform in the 1840s was followed by a hiatus of about 80 years before other inhaled anesthetics were introduced (Figure 4.1).¹ In 1950, all inhaled anesthetics, with the exception of nitrous oxide, were flammable or potentially toxic to the liver. Recognition that replacing a hydrogen atom with a fluorine atom decreased flammability led to the introduction, in 1951, of the first halogenated hydrocarbon anesthetic, fluroxene. Fluroxene was used clinically for several years before its voluntary withdrawal from the market due to its potential flammability and increasing evidence that this drug could cause organ toxicity.²

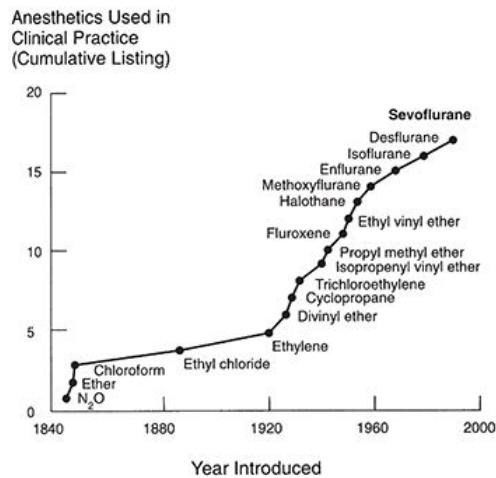


FIGURE 4.1 Inhaled anesthetics introduced into clinical practice beginning with the successful use of nitrous oxide in 1844 for dental anesthesia followed by recognition of the anesthetic properties of ether in 1846 and of chloroform in 1847. Modern anesthetics, beginning with halothane, differ from prior anesthetics in being fluorinated and nonflammable. *Derived from Eger EI. Desflurane (Suprane): A Compendium and Reference. Nutley, NJ: Anaquest; 1993:1-119.*

Halothane was synthesized in 1951 and introduced for clinical use in 1956. However, the tendency for alkane derivatives such as halothane to enhance the arrhythmogenic effects of epinephrine led to the search for new inhaled anesthetics derived from ethers. Methoxyflurane, a methyl ethyl ether, was the first such derivative. Methoxyflurane was introduced into clinical practice in 1960. Although methoxyflurane did not enhance the arrhythmogenic effects of epinephrine, its high solubility in blood and lipids resulted in a prolonged induction and slow recovery from anesthesia. More importantly, methoxyflurane caused hepatic toxicity. Extensive hepatic metabolism increased plasma concentrations of fluoride, which caused nephrotoxicity, especially with prolonged exposures to the anesthetic. Methoxyflurane has analgesic properties at concentrations far below those that induce anesthesia. Although its use was abandoned in the United States and Canada in the 1970s, it continues to be used in Australia for brief painful procedures and emergency transport.³ Enflurane, the next methyl ethyl ether derivative, was introduced for clinical use in 1973. This anesthetic, in contrast to halothane, does not enhance the arrhythmogenic effects of epinephrine or cause hepatotoxicity. Nevertheless, side effects were present, including metabolism to inorganic fluoride and stimulation of the central nervous system (CNS), lowering the seizure threshold. In search of a drug with fewer side effects, isoflurane, a structural isomer of enflurane, was introduced in 1981. This drug was resistant to metabolism, making organ toxicity unlikely after its administration.

Inhaled Anesthetics for the Present and Future

The search for even more pharmacologically “perfect” inhaled anesthetics did not end with the introduction and widespread use of isoflurane. The exclusion of all halogens except fluorine results in nonflammable liquids that are poorly lipid soluble and extremely resistant to metabolism. Desflurane, a totally fluorinated methyl ethyl ether, was introduced in 1992 and was followed in 1994 by the totally fluorinated methyl isopropyl ether, sevoflurane.^{4,5} The low solubility of these volatile anesthetics in blood facilitated rapid induction of anesthesia, precise control of end-tidal anesthetic concentrations during maintenance of anesthesia, and prompt recovery at the end of anesthesia independent of the duration of administration. The development, introduction, and rapid clinical acceptance of desflurane and sevoflurane reflects market forces (ambulatory surgery and the desire for rapid awakening possible with poorly soluble but potent anesthetics) more than an improved pharmacologic profile on various organ systems as compared with isoflurane. The challenge to the anesthesiologist is to exploit the pharmacokinetic advantages of these drugs while minimizing the risks (airway irritation, sympathetic nervous system stimulation, carbon monoxide production from interaction with carbon dioxide absorbent and complex vaporizer technology with desflurane, and compound A production from sevoflurane) and the increased expense associated with the manufacture and increased cost of administration of desflurane and sevoflurane.

Cost Considerations

Cost is an important consideration in the adoption of new drugs, including inhaled anesthetics. Factors that may influence the cost of a new inhaled anesthetics include (1) price (cost per milliliter of liquid); (2) inherent characteristics of the anesthetic, such as its vapor pressure (milliliter of vapor available per milliliter of liquid), potency, and solubility; and (3) fresh gas flow rate selected for delivery of the anesthetic.⁶ The costs of new inhaled anesthetics can be decreased by using low fresh gas flow rates. Less soluble anesthetics are more suitable for use with low gas flow rates because their poor solubility permits better control of the delivered concentration. Furthermore, there is less depletion of these anesthetics from the inspired gases so that fewer molecules need to be added to the returning rebreathed gases. This conservation offsets the decreased potency of a drug such as desflurane compared with isoflurane. For example, desflurane is one-fifth as potent as isoflurane; yet, the amount of desflurane that must be delivered to sustain minimal alveolar concentration (MAC) is only slightly more than threefold the amount of isoflurane. Similarly, although MAC of sevoflurane is 74% greater than isoflurane, the amount of sevoflurane that must be delivered to sustain MAC is only 30% greater.

Current Clinically Useful Inhaled Anesthetics

Commonly administered inhaled anesthetics include the inorganic gas nitrous oxide and the volatile liquids isoflurane, desflurane, and sevoflurane (**Table 4.1**) (**Figure 4.2**).^{4,5} Halothane and enflurane are administered infrequently but are included in the discussion of the comparative pharmacology of volatile anesthetics because halothane in particular has been studied extensively.^{4,5}

TABLE 4.1

Physical and chemical properties of inhaled anesthetics

	Nitrous oxide	Halothane	Enflurane	Isoflurane	Desflurane	Sevoflurane
Molecular weight	44	197	184	184	168	200
Boiling point (°C)		50.2	56.5	48.5	22.8	58.5
Vapor pressure (mm Hg; 20°C)	Gas	244	172	240	669	170
Odor	Sweet	Organic	Ethereal	Ethereal	Ethereal	Ethereal
Preservative necessary	No	Yes	No	No	No	No
Stability in soda lime (40°C)	Yes	No	Yes	Yes	Yes	No
Blood:gas partition coefficient	0.46	2.54	1.90	1.46	0.42	0.69
	104	0.75	1.63	1.17	6.6	1.80

MAC (37°C, 30-55 years old, P_B 760 mm Hg) (%)

Abbreviations: MAC, minimal alveolar concentration; P_B, brain partial pressure.

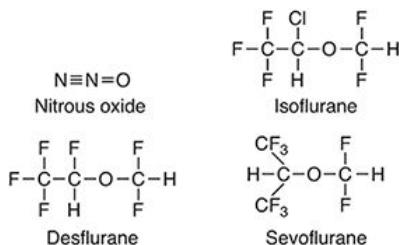


FIGURE 4.2 Inhaled anesthetics.

Volatile liquids are administered as vapors after their vaporization in devices known as **vaporizers**. Diethyl ether and chloroform are still available but mostly used only in veterinary medicine. Xenon is an inert gas with anesthetic properties, but its clinical use is hindered by its high cost.⁷

Nitrous Oxide

Nitrous oxide is a low-molecular-weight, odorless to sweet-smelling nonflammable gas of low potency and poor blood solubility (blood:gas partition coefficient 0.46) that is most commonly administered in combination with opioids or volatile anesthetics to produce general anesthesia. Although nitrous oxide is nonflammable, it will support combustion.⁸ Its poor blood solubility permits rapid achievement of an alveolar and brain partial pressure of the drug (Figure 4.3).^{9,10} The analgesic effects of nitrous oxide are prominent but short lived, dissipating after about 20 minutes of use while sedative effects persist.¹¹ Nitrous oxide causes minimal skeletal muscle relaxation. Nitrous oxide has no effect on tissue PO₂ measurements but does cause a small increase in the P₅₀ (about 1.6 mm Hg).¹² Nitrous oxide has not only acute analgesic activity but may also attenuate hyperacute hyperalgesia by remifentanil¹⁰ and have efficacy to reduce chronic pain.¹³

The benefits of nitrous oxide must be balanced against its possible adverse effects related to the high-volume absorption of nitrous oxide in gas-containing spaces, ability to inactivate vitamin B₁₂ that may be relevant in patients with depleted reserves or related genetic defects in the vitamin B₁₂ pathway. The impact of nitrous oxide on postoperative nausea and vomiting is a topic that evokes passionate fixed beliefs in many anesthesia practitioners for unclear reasons¹⁴ as it has been well studied. When used as part of some anesthetic techniques, nitrous oxide increases the incidence of nausea and vomiting. A 2010 meta-analysis that included 30 published studies of many anesthetic regimens suggests that avoidance of nitrous oxide is associated with a lower risk of postoperative nausea and vomiting (relative risk = 0.80 [0.71-0.90], p = 0.0003).¹⁵ However, the capacity of nitrous oxide to increase the likelihood of postoperative nausea and vomiting needs to be considered in light of the alternatives. Many practitioners eschew nitrous oxide in light of the postoperative nausea and vomiting risk but have no concerns about using volatile anesthetics. An elegant factorial trial published in *The New England Journal of Medicine* in 2004 (the IMPACT trial) put this issue into clinical context.¹⁶ This was a study of young women having gynecologic surgery at high risk for nausea and vomiting. Without any antiemetic, approximately 60% had nausea and vomiting when anesthetized with volatile anesthetic alone, volatile anesthetic with nitrous oxide, or propofol with nitrous oxide. The only anesthetic with significantly reduced incidence of nausea and vomiting was propofol alone. The addition of a single antiemetic reduced the incidence of postoperative nausea and vomiting to approximately 35% with the exception of a volatile anesthetic with nitrous oxide that was 45%. Environmental considerations are addressed later in the chapter.

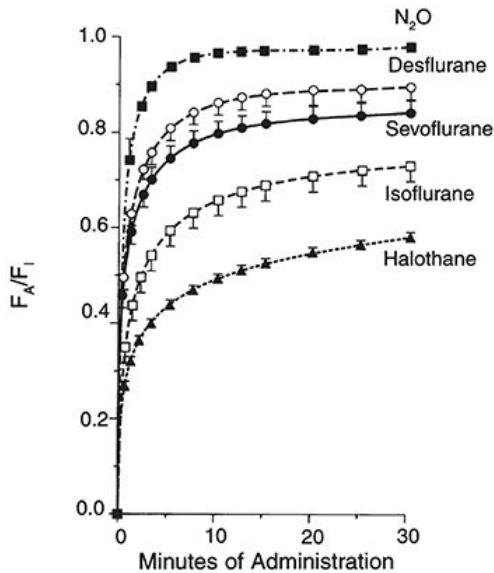


FIGURE 4.3 The pharmacokinetics of inhaled anesthetics during the induction of anesthesia is defined as the ratio of the end-tidal anesthetic concentration (F_A) to the inspired anesthetic concentration (F_I). Consistent with their relative blood:gas partition coefficients, the F_A/F_I of poorly soluble anesthetics (nitrous oxide, desflurane, sevoflurane) increases more rapidly than that of anesthetics with greater solubility in blood. A decrease in the rate of change in the F_A/F_I after 5 to 15 minutes (three time constants) reflects decreased tissue uptake of the anesthetic as the vessel-rich group tissues become saturated. (Data are mean \pm standard deviation.) Reprinted with permission from Yasuda N, Lockhart SH, Eger EI, et al. Comparison of kinetics of sevoflurane and isoflurane in humans. Anesth Analg. 1991;72(3):316-324. Copyright © 1991 International Anesthesia Research Society.

Halothane

Halothane is a halogenated alkane derivative that exists as a clear, nonflammable liquid at room temperature. The vapor of this liquid has a sweet, bland odor. An intermediate solubility in blood, combined with a high potency, permits intermediate onset and recovery from anesthesia using halothane alone or in combination with nitrous oxide or injected drugs such as opioids.

Halothane was developed on the basis of predictions that its halogenated structure would provide intermediate blood solubility, anesthetic potency, and molecular stability and avoid flammability. Specifically, carbon-fluorine bond decreases flammability, and the trifluorocarbon contributes to molecular stability. The presence of a carbon-chlorine and carbon-bromine bond plus the retention of a hydrogen atom ensures anesthetic potency. Despite its chemical stability, halothane is susceptible to decomposition to hydrochloric acid, hydrobromic acid, chloride, bromide, and phosgene. For this reason, halothane is stored in amber-colored bottles, and thymol is added as a preservative to prevent spontaneous oxidative decomposition. Thymol that remains in vaporizers after vaporization of halothane can cause vaporizer turnstiles or temperature-compensating devices to malfunction.

Enflurane

Enflurane is no longer in common use in the United States. It is a halogenated methyl ethyl ether that exists as a clear, nonflammable volatile liquid at room temperature and has a pungent, ethereal odor. Its intermediate solubility in blood combined with a high potency permits intermediate onset and recovery from anesthesia, using enflurane alone or in combination with nitrous oxide or injected drugs such as opioids. Enflurane decreases the threshold for seizures. Enflurane is oxidized in the liver to produce inorganic fluoride ions that can be nephrotoxic. It was primarily used for procedures in which a low threshold for seizure generation is desirable, such as electroconvulsive therapy.

Isoflurane

Isoflurane is a halogenated methyl ethyl ether that exists as a clear, nonflammable liquid at room temperature and has a pungent, ethereal odor. Its intermediate solubility in blood combined with a high potency permits intermediate onset and recovery from anesthesia using isoflurane alone or in combination with nitrous oxide or injected drugs such as opioids.

Isoflurane is characterized by extreme physical stability, undergoing no detectable deterioration during 5 years of storage or on exposure to carbon dioxide absorbents or sunlight. The stability of isoflurane obviates the need to add preservatives such as thymol to the commercial preparation.

Desflurane

Desflurane is a fluorinated methyl ethyl ether that differs from isoflurane only by substitution of a fluorine atom for the chlorine atom found on the alpha-ethyl component of isoflurane. Fluorination rather than chlorination increases vapor pressure (decreases intermolecular attraction), enhances molecular stability, and decreases potency. Indeed, the vapor pressure of desflurane exceeds that of isoflurane by a factor of three such that desflurane would boil at normal operating room temperatures. A new vaporizer technology addressed this property, producing a regulated concentration by converting desflurane to a gas (heated and pressurized vaporizer that requires electrical power), which is then blended with diluent fresh gas flow. The only evidence of metabolism of desflurane is the presence of measurable concentrations of serum and urinary trifluoroacetate that are one-fifth to one-tenth those produced by the metabolism of isoflurane. The potency of desflurane as reflected by MAC is about fivefold less than isoflurane.

Unlike halothane and sevoflurane, desflurane is pungent, making it unlikely that inhalation induction of anesthesia would be feasible or pleasant for the patient. Indeed, the pungency of desflurane produces airway irritation and an appreciable incidence of salivation, breath holding, coughing, or laryngospasm when >6% inspired desflurane is administered to an awake patient.⁴ Carbon monoxide results from degradation of desflurane by the strong base present in desiccated carbon dioxide absorbents. Desflurane produces the highest carbon monoxide concentrations, followed by enflurane and isoflurane, whereas amounts produced from halothane and sevoflurane are trivial.

Intraoperative Diagnosis of Carbon Monoxide Poisoning

Intraoperative detection of carbon monoxide is difficult because pulse oximetry cannot differentiate between carboxyhemoglobin and oxyhemoglobin. Moderately decreased pulse oximetry readings despite adequate arterial partial pressures of oxygen (especially during the first case of the day, “Monday morning phenomena”) should suggest the possibility of carbon monoxide exposure and the need to measure carboxyhemoglobin.¹⁷ Furthermore, there is no routinely available means to reliably identify the presence of carbon monoxide in the breathing circuit or to detect when carbon dioxide absorbent has become desiccated (absorbent color change does not occur in response to desiccation or carbon monoxide formation). In addition to decreased pulse oximeter readings, an erroneous gas analyzer reading (indicates mixed gas readings or enflurane when desflurane is being administered) has been described as an early indirect warning of carbon monoxide formation.^{18,19} This erroneous gas analyzer reading was attributed to trifluoromethane, which is produced along with carbon monoxide by degradation of isoflurane, enflurane, and desflurane but not sevoflurane. Trifluoromethane has an infrared absorption profile similar to enflurane resulting in the gas analyzer indicating administration of this volatile anesthetic when the vaporizer is known to contain desflurane or isoflurane. An erroneous gas analyzer reading as an early warning of carbon monoxide exposure does not occur during administration of sevoflurane.¹⁸ Carboxyhemoglobin can be measured acutely with CO-oximetry; this technology is routinely available.²⁰ Delayed neurophysiologic sequelae due to carbon monoxide poisoning (cognitive defects, personality changes, gait disturbances) may occur as late as 3 to 21 days after anesthesia. Intraoperative hemolysis has the potential to result in carbon monoxide exposure, which can mimic carbon monoxide production from degradation of volatile anesthetics.²¹

Solubility characteristics (blood:gas partition coefficient 0.45) and potency (MAC 6.6%) permit rapid achievement of an alveolar partial pressure necessary for anesthesia followed by prompt awakening when desflurane is discontinued. It is this lower blood-gas solubility and more precise control over the delivery of

anesthesia and more rapid recovery from anesthesia that distinguish desflurane (and sevoflurane) from earlier volatile anesthetics.

Sevoflurane

Sevoflurane is a fluorinated methyl isopropyl ether. The vapor pressure of sevoflurane resembles that of halothane and isoflurane, permitting delivery of this anesthetic via a conventional unheated vaporizer. The solubility of sevoflurane (blood:gas partition coefficient 0.69) resembles that of desflurane, ensuring prompt induction of anesthesia and recovery after discontinuation of the anesthetic. Compared with isoflurane, recovery from sevoflurane anesthesia is 3 to 4 minutes faster and the difference is magnified in longer duration surgical procedures (>3 hours) (**Figure 4.4**).²² Sevoflurane is nonpungent, has minimal odor, produces bronchodilation similar in degree to isoflurane, and causes the least degree of airway irritation among the currently available volatile anesthetics. For these reasons, sevoflurane, like halothane, is acceptable for inhalation induction of anesthesia.

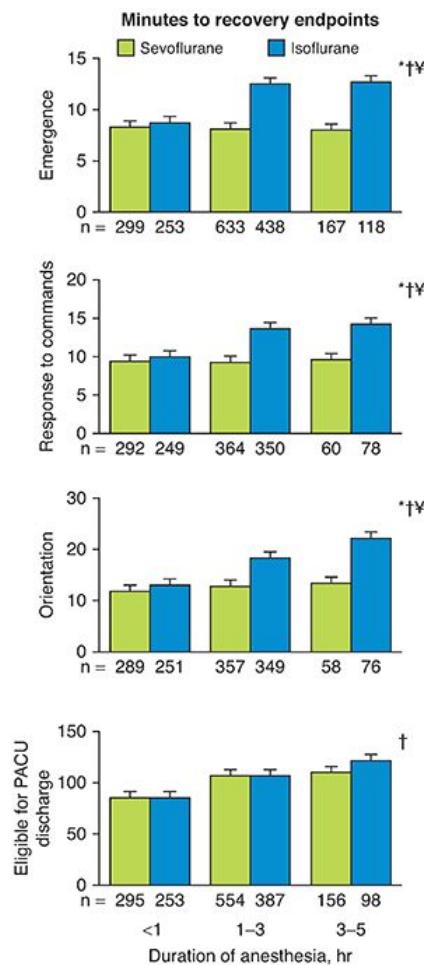


FIGURE 4.4 Times to emergence, responses to commands, orientation, and discharge from the postanesthesia care unit (PACU) are presented with minutes to end point on the y-axis and number of patients studied and duration of anesthesia on the x. (Data are mean \pm standard error of the mean.) Abbreviations: n, number of patients studied; *, significant difference between sevoflurane and isoflurane; †, significant difference with increasing duration of anesthesia; ‡, significant interaction between anesthetic and duration of anesthesia. Reprinted with permission from Ebert TJ, Robinson BJ, Uhrich TD, et al. Recovery from sevoflurane anesthesia: a comparison to isoflurane and propofol anesthesia. *Anesthesiology*. 1998;89(6):1524-1531. Copyright © 1998 American Society of Anesthesiologists, Inc.

Sevoflurane may be 100-fold more vulnerable to metabolism than desflurane, with an estimated 3% to 5% of the dose undergoing biodegradation. The resulting metabolites include inorganic fluoride (plasma concentrations exceed those that occur after enflurane) and hexafluoroisopropanol. Sevoflurane metabolism does not result in the formation of trifluoroacetylated liver proteins and therefore cannot stimulate the formation of antitrifluoroacetylated protein antibodies. In this regard, sevoflurane differs from halothane, enflurane, isoflurane, and desflurane, all of which are metabolized to reactive acyl halide intermediates with the potential to produce hepatotoxicity as well as cross-sensitivity between drugs.²³ Sevoflurane is the least likely volatile anesthetic to form carbon monoxide on exposure to carbon dioxide absorbents. In contrast to other volatile anesthetics, sevoflurane breaks down in the presence of the strong bases present in carbon dioxide absorbents to form compounds that are toxic in animals (**Figure 4.5**).⁵ The principal degradation product is fluoromethyl-2,2-difluoro-1-(trifluoromethyl) vinyl-ether (compound A). Although nephrotoxic in animal studies, the levels of these compounds (principally compound A) that occur during administration of sevoflurane to patients are far below speculated toxic levels, even when total gas flows are 1 L per minute.^{23,24}

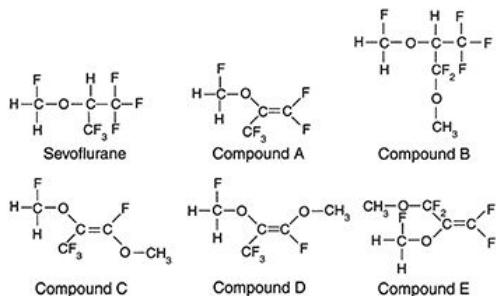


FIGURE 4.5 Degradation products of sevoflurane on exposure to soda lime. The formation of these degradation products is increased under experimental conditions in which the soda lime is heated to $\geq 65^{\circ}\text{C}$.

Xenon

Xenon is an inert gas with many of the characteristics considered important for an ideal inhaled anesthetic.⁷ The MAC is 63% to 71% in humans, suggesting that this gas is more potent than nitrous oxide (MAC 104%).²⁵ The MAC-awake for xenon is 33%.²⁶ Unlike MAC for other volatile anesthetics, there is evidence that xenon MAC is gender dependent, being less in females.²⁷ Xenon is nonexplosive, odorless, and chemically inert as reflected by absence of metabolism and low toxicity. Unlike other inhaled anesthetics, it is not harmful to the environment because it is prepared by fractional distillation of the atmospheric air. To date, its high cost has hindered its acceptance in anesthesia practice. This disadvantage may be offset to some degree by using low fresh gas flow rates and development of a xenon-recycling system. Nevertheless, even if cost considerations can be negated, acceptance of xenon as a replacement for current inhaled anesthetics (that also share many of the same advantages of xenon) would be based more on evidence of special properties or that morbidity and mortality is considerably less when this drug is administered during anesthesia.⁷

Xenon has a blood:gas partition coefficient of 0.115, which is lower than that of other clinically useful anesthetics and even lower than that of nitrous oxide (0.46), sevoflurane (0.69), and desflurane (0.42). Like nitrous oxide, xenon anesthesia results in gas exchange conditions that favor air bubble expansion, which could worsen neurologic injury from venous air embolism.²⁸ Diffusion of xenon into highly compliant bowel occurs but is less compared with nitrous oxide (**Figure 4.6**).²⁹ It is possible this minimal effect on bowel may be different when xenon diffuses into less compliant cavities as represented by pneumothorax, pneumoperitoneum, and pneumopericardium. Xenon does not trigger malignant hyperthermia in susceptible swine.³⁰ Emergence from xenon anesthesia, regardless of the duration of anesthesia, is 2 to 3 times faster than that from equal-MAC nitrous oxide plus isoflurane or sevoflurane.³¹ Xenon is a potent hypnotic and analgesic, resulting in suppression of hemodynamic and catecholamine responses to surgical stimulation. Unlike other inhaled and injected anesthetics, xenon does not produce hemodynamic depression in healthy

adults. Neuromuscular-blocking effects of rocuronium are not different when given during propofol versus xenon anesthesia.³² A risk of recall would seem to be present but has not been observed in small numbers of patients. Like ketamine, xenon exerts antagonist effects at *N*-methyl-D-aspartate (NMDA) subtypes of glutamate receptors, which have been shown to have both neuroprotective and neurotoxic properties. Xenon is unique among known NMDA antagonists in exhibiting neuroprotection without coexisting psychotomimetic behavioral changes perhaps because it does not stimulate dopamine release from the nucleus accumbens.³³ The reason why ketamine and nitrous oxide, but not xenon, produce neurotoxicity may reflect actions on dopaminergic pathways that do not occur in the presence of xenon.

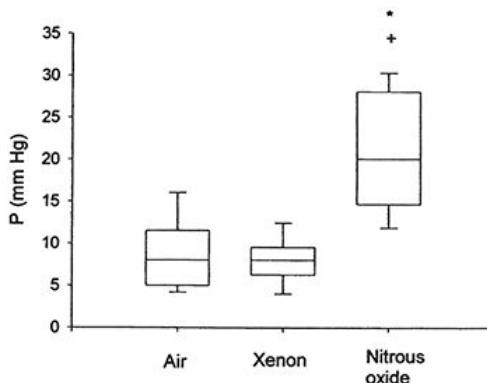


FIGURE 4.6 Pressures in obstructed bowel segments after 4 hours of air or anesthesia administration. After 4 hours of anesthesia, intraluminal pressures were significantly higher in the presence of nitrous oxide. Abbreviations: +, nitrous oxide compared to control; *, nitrous oxide compared to xenon. Reprinted with permission from Reinelt H, Schirmer U, Marx T, et al. Diffusion of xenon and nitrous oxide into the bowel. Anesthesiology. 2001;94(3):475-477. Copyright © 2001 American Society of Anesthesiologists, Inc.

Pharmacokinetics of Inhaled Anesthetics

The pharmacokinetics of inhaled anesthetics describes their (1) absorption (uptake) from alveoli into pulmonary capillary blood, (2) distribution in the body, (3) metabolism, and (4) elimination, principally via the lungs. The pharmacokinetics of volatile anesthetics may be influenced by aging, reflecting decreases in lean body mass and increases in body fat.³⁴ The volume of distribution of the central compartment (plasma volume) is smaller, whereas the apparent volume of distribution (steady state) for these drugs in the elderly is larger, especially for those anesthetics most soluble in fat. In addition, impaired pulmonary gas exchange may decrease anesthetic clearance with age. Furthermore, reduced cardiac output in the elderly decreases tissue perfusion, increases time constants, and may be associated with an altered regional distribution of anesthetics.

A series of partial pressure gradients beginning at the anesthetic machine serve to propel the inhaled anesthetic across various barriers (alveoli, capillaries, cell membranes) to their sites of action in the CNS. The principal objective of inhalation anesthesia is to achieve a constant and optimal brain partial pressure of the inhaled anesthetic.

The brain and all other tissues equilibrate with the partial pressures of inhaled anesthetics delivered to them by arterial blood (P_a). Likewise, arterial blood equilibrates with the alveolar partial pressures (P_A) of anesthetics. This emphasizes that the P_A of inhaled anesthetics mirrors the brain partial pressure (P_{BRAIN}) at steady state. This is the reason that P_A is used as an index of (1) depth of anesthesia, (2) recovery from anesthesia, and (3) anesthetic equal potency (MAC). It is important to recognize that equilibration between the two phases means the same partial pressure exists in both phases. Equilibration does not mean equality of concentrations in two biophases. Understanding those factors that determine the P_A and thus the P_{BRAIN} permits control of the doses of inhaled anesthetics delivered to the brain to maintain a constant and optimal depth of anesthesia. This relationship is applicable because volatile anesthetics are only minimally metabolized and as such are excreted from the lung. The availability of an “online” readout of end-tidal

partial pressure, which at equilibrium matches brain partial pressure, makes volatile anesthetic dosing easier than intravenous anesthetic dosing.

Determinants of Alveolar Partial Pressure

The PA and ultimately the P_{BRAIN} of inhaled anesthetics are determined by input (delivery) into alveoli minus uptake (loss) of the drug from alveoli into arterial blood ([Table 4.2](#)). Input of anesthetics into alveoli depends on the (1) inhaled partial pressure (PI), (2) alveolar ventilation, and (3) characteristics of the anesthetic breathing (delivery) system. Uptake of inhaled anesthetics from alveoli into the pulmonary capillary blood depends on (1) solubility of the anesthetic in body tissues, (2) cardiac output, and (3) alveolar-to-venous partial pressure differences (A-vD).

TABLE 4.2

Factors determining partial pressure gradients necessary for establishment of anesthesia
Transfer of inhaled anesthetic from anesthetic machine to alveoli (anesthetic input)
Inspired partial pressure
Alveolar ventilation
Characteristics of anesthetic breathing system
Functional residual capacity
Transfer of inhaled anesthetic from alveoli to arterial blood (anesthetic loss)
Blood:gas partition coefficient
Cardiac output
Alveolar-to-venous partial pressure difference
Transfer of inhaled anesthetic from arterial blood to brain (anesthetic loss)
Brain:blood partition coefficient
Cerebral blood flow
Arterial-to-venous partial pressure difference

Inhaled Partial Pressure

A high PI delivered from the anesthetic machine is required during initial administration of the anesthetic. A high initial input offsets the impact of uptake, accelerating induction of anesthesia as reflected by the rate of rise in the PA and thus the P_{BRAIN} . With time, as uptake into the blood decreases, the PI should be decreased to match the decreased anesthetic uptake and therefore maintain a constant and optimal P_{BRAIN} . If the PI is maintained constant with time, the PA and P_{BRAIN} will increase progressively as uptake diminishes.

Concentration Effect

The impact of PI on the rate of rise of the PA of an inhaled anesthetic is known as the **concentration effect** ([Figure 4.7](#)).³⁵ The concentration effect states that the higher the PI, the more rapidly the PA approaches the PI. The higher PI provides anesthetic molecule input to offset uptake and thus speeds the rate at which the PA increases.

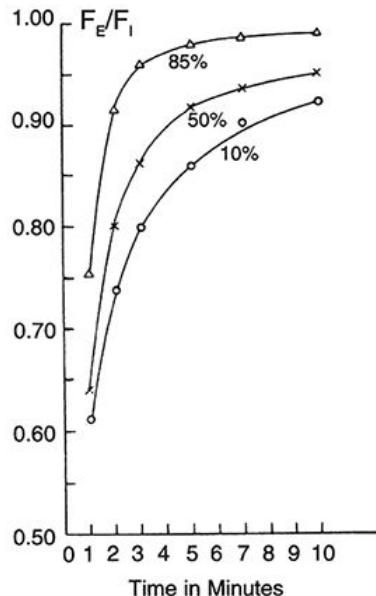


FIGURE 4.7 The impact of the inhaled concentration of an anesthetic on the rate at which the alveolar concentration increases toward the inspired (F_E/F_I) is known as the *concentration effect*. Reprinted with permission from Eger EI. Effect of inspired anesthetic concentration on the rate of rise of alveolar concentration. Anesthesiology. 1963;24(2):153-157. Copyright © 1963 American Society of Anesthesiologists, Inc.

The concentration effect results from (1) a concentrating effect and (2) an augmentation of tracheal inflow.³⁶ The concentrating effect reflects concentration of the inhaled anesthetic in a smaller lung volume due to uptake of all gases in the lung. At the same time, anesthetic input via tracheal inflow is increased to fill the space (void) produced by uptake of gases.

Second-Gas Effect

The second-gas effect reflects the ability of high-volume uptake of one gas (first gas) to accelerate the rate of increase of the PA of a concurrently administered “companion” gas (second gas) (Figure 4.8).³⁷ For example, the initial large-volume uptake of nitrous oxide accelerates the uptake of companion (second) gases such as oxygen and volatile anesthetics. This increased uptake of the second gas reflects increased tracheal inflow of all the inhaled gases (first and second gases) and higher concentration of the second gas or gases in a smaller lung volume (concentrating effect) due to the high-volume uptake of the first gas (Figure 4.9).³⁶ Conceptually, the loss of lung volume may be compensated for by decreased expired ventilation as well as increased inspired ventilation (increased tracheal inflow). The implication that extra gas is routinely drawn into the lungs to compensate for loss of lung volume is misleading if compensatory changes include decreased expired ventilation and/or a decrease in lung volume.³⁸

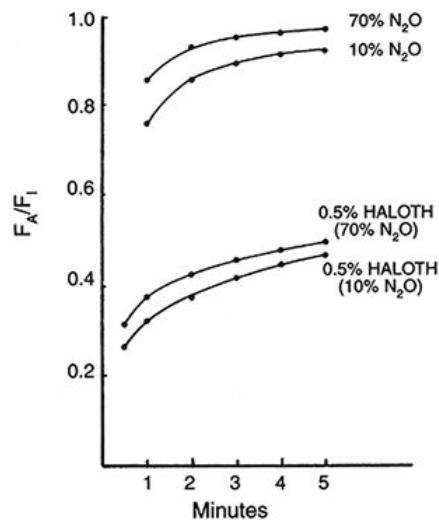


FIGURE 4.8 The second-gas effect is the accelerated increase in the alveolar concentration of a second gas, halothane (HALOTH), toward the inspired (F_A/F_I) in the presence of a high inhaled concentration of the first gas (nitrous oxide [N_2O]). Reprinted with permission from Epstein RM, Rackow H, Salanitre E, et al. *Influence of the concentration effect on the uptake of anesthetic mixtures: the second gas effect.* Anesthesiology. 1964;25(3):364-371. Copyright © 1964 American Society of Anesthesiologists, Inc.

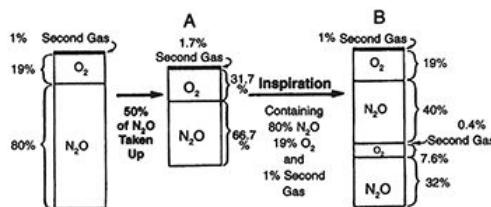


FIGURE 4.9 The second-gas effect results from a concentrating effect (A) and an augmentation of tracheal inflow (B). Abbreviations: O_2 , oxygen; N_2O , nitrous oxide. Reprinted with permission from Stoelting RK, Eger EI II. *An additional explanation for the second gas effect: a concentrating effect.* Anesthesiology. 1969;30(3):273-277. Copyright © 1969 American Society of Anesthesiologists, Inc.

Alveolar Ventilation

Increased alveolar ventilation, like PI, promotes input of anesthetics to offset uptake. The net effect is a more rapid rate of increase in the PA toward the PI and thus induction of anesthesia. In addition to the increased input, the decreased P_{CO_2} produced by hyperventilation of the lungs decreases cerebral blood flow (CBF). Conceivably, the impact of increased input on the rate of rise of the PA would be offset by decreased delivery of anesthetic to the brain. Decreased alveolar ventilation decreases input and thus slows the establishment of a PA and P_{BRAIN} necessary for the induction of anesthesia. The greater the alveolar ventilation to functional residual capacity (FRC) ratio, the more rapid is the rate of increase in the PA. In neonates, this ratio is approximately 5:1 compared with only 1.5:1 in adults, reflecting the greater metabolic rate in neonates compared with adults. As a result, the rate of increase of PA toward the PI and thus the induction of anesthesia is more rapid in neonates than in adults (Figure 4.10).³⁹

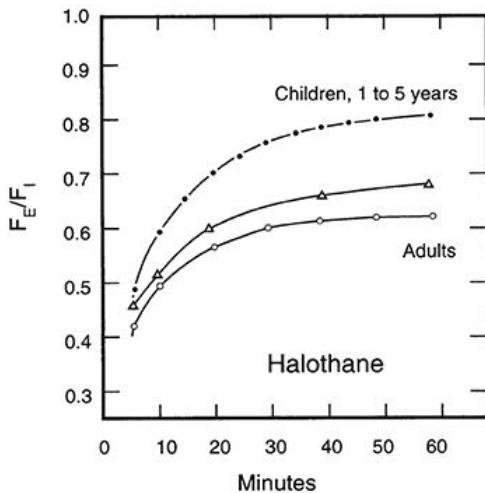


FIGURE 4.10 The rate at which the alveolar concentration (F_E) increases toward the inspired (F_I) for halothane (HALO 0.5%) in children 1 to 5 years of age is more rapid than in adults. *Reprinted with permission from Salanitre E, Rackow H. The pulmonary exchange of nitrous oxide and halothane in infants and children. Anesthesiology. 1969;30(4):388-394. Copyright © 1969 American Society of Anesthesiologists, Inc.*

Spontaneous Versus Mechanical Ventilation

Inhaled anesthetics influence their own uptake by virtue of dose-dependent depressant effects on alveolar ventilation. This, in effect, is a negative feedback protective mechanism that prevents establishment of an excessive depth of anesthesia (delivery of anesthesia is decreased when ventilation is decreased) when a high PI is administered during spontaneous breathing (Figure 4.11).⁴⁰ As anesthetic input decreases in parallel with decreased ventilation, anesthetic present in tissues is redistributed from tissues in which it is present in high concentrations (brain) to other tissues in which it is present in low concentrations (skeletal muscles). When the concentration (partial pressure) in the brain decreases to a certain threshold, ventilation increases and delivery of the anesthetic to the lungs increases. This protective mechanism against development of an excessive depth of anesthesia (anesthetic overdose) is lost when mechanical ventilation of the lungs replaces spontaneous breathing.

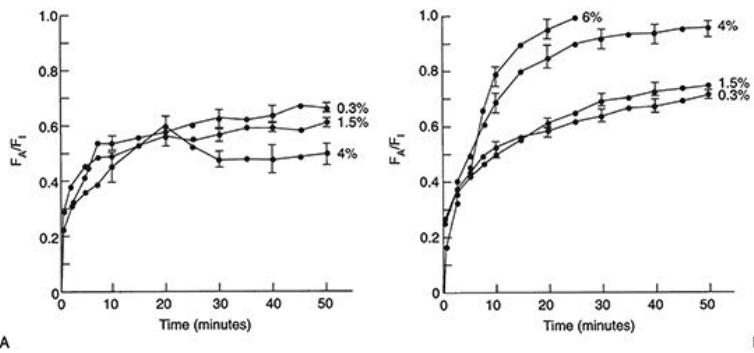


FIGURE 4.11 Effect of the mode of ventilation on the rate of increase of the alveolar concentration (F_A) of halothane toward the inspired concentration (F_I) as determined in an animal model. Negative feedback inhibition of spontaneous ventilation (A) limits the F_A/F_I to 0.6 for all the inspired concentrations of halothane. The positive feedback effect of controlled ventilation (B) results in ratios of the F_A/F_I that approach 1.0 and excessive depressant effects of halothane on the cardiovascular system at the higher inspired concentrations of the anesthetic. (Data are mean \pm standard deviation.) *Reprinted with permission from Gibbons RT, Steffey EP, Eger EI. The effect of spontaneous versus controlled ventilation on the rate of*

rise of the alveolar halothane concentration in dogs. Anest Analg. 1977;56(1):32-34. Copyright © 1977 International Anesthesia Research Society.

Impact of Solubility

The impact of changes in alveolar ventilation on the rate of increase in the PA toward the PI depends on the solubility of the anesthetic in blood. For example, changes in alveolar ventilation influence the rate of increase of the PA of a soluble anesthetic (halothane, isoflurane) more than a poorly soluble anesthetic (nitrous oxide, desflurane, sevoflurane). Indeed, the rate of increase in the PA of nitrous oxide is rapid regardless of the alveolar ventilation. This occurs because uptake of nitrous oxide is limited because of its poor solubility in blood. Conversely, uptake of a more blood-soluble anesthetic is larger, and increasing alveolar ventilation will accelerate the rate at which the PA of the soluble anesthetic approaches the PI. This emphasizes that changing from spontaneous breathing to mechanical (controlled) ventilation of the lungs, which also is likely to be associated with increased alveolar ventilation, will probably increase the depth of anesthesia (PA) produced by a more blood-soluble anesthetic.

Anesthetic Breathing System

Characteristics of the anesthetic breathing system that influence the rate of increase of the PA are the (1) volume of the external breathing system, (2) solubility of the inhaled anesthetics in the rubber or plastic components of the breathing system, and (3) gas inflow from the anesthetic machine. The volume of the anesthetic breathing system acts as a buffer to slow achievement of the PA. High gas inflow rates (5-10 L per minute) from the anesthetic machine negate this buffer effect. Solubility of inhaled anesthetics in the components of the anesthetic breathing system initially slows the rate at which the PA increases. At the conclusion of the administration of an anesthetic, however, reversal of the partial pressure gradient in the anesthetic breathing system results in elution of the anesthetic, which slows the rate at which the PA decreases.

Solubility

The solubility of the inhaled anesthetics in blood and tissues is denoted by the partition coefficient ([Table 4.3](#)).¹⁴¹ A partition coefficient is a distribution ratio describing how the inhaled anesthetic distributes itself between two phases at equilibrium (partial pressures equal in both phases). For example, a blood:gas partition coefficient of 0.5 means that the concentration of inhaled anesthetic in the blood is half that present in the alveolar gases when the partial pressures of the anesthetic in these two phases is identical. Similarly, a brain:blood partition coefficient of 2 indicates a concentration of anesthetic in the brain is twice that in the blood when the partial pressures of anesthetic are identical at both sites.

TABLE 4.3

Comparative solubilities of inhaled anesthetics^a

	Blood:gas partition coefficient	Brain:blood partition coefficient	Muscle:blood partition coefficient	Fat:blood partition coefficient	Oil:gas partition coefficient
Soluble					
Methoxyflurane	12	2	1.3	48.8	970
Intermediately soluble					
Halothane	2.54	1.9	3.4	51.1	224
Enflurane	1.90	1.5	1.7	36.2	98
Isoflurane	1.46	1.6	2.9	44.9	98
Poorly soluble					
Nitrous oxide	0.46	1.1	1.2	2.3	1.4
Desflurane	0.42	1.3	2.0	27.2	18.7

Sevoflurane	0.69	1.7	3.1	47.5	55
Xenon	0.115				

^aData from Eger EI II. *Desflurane (Suprane): A Compendium and Reference*. Nutley, NJ: Anaquest; 1993; Yasuda N, Targ AC, Eger EI II. Solubility of I-653, sevoflurane, isoflurane, and halothane in human tissues. *Anesth Analg*. 1989;69:370-373.

Partition coefficients may be thought of as reflecting the relative capacity of each phase to accept anesthetic. Partition coefficients are temperature dependent such that the solubility of a gas in a liquid is decreased when the temperature of the liquid increases.

Blood:Gas Partition Coefficients

The rate of increase of the PA toward the PI (maintained constant by mechanical ventilation of the lungs) is inversely related to the solubility of the anesthetic in blood (see [Figure 4.3](#)).^{42,43} Based on their blood:gas partition coefficients, inhaled anesthetics are categorized traditionally as soluble, intermediately soluble, and poorly soluble (see [Table 4.3](#)).^{1,41} Blood can be considered a pharmacologically inactive reservoir, the size of which is determined by the solubility of the anesthetic in blood. When the blood:gas partition coefficient is high, a large amount of anesthetic must be dissolved in the blood before the Pa equilibrates with the PA. For example, the high blood solubility of methoxyflurane slows the rate at which the PA and Pa increase relative to the PI, and the induction of anesthesia is slow. The impact of high blood solubility on the rate of increase of the Pa can be offset to some extent by increasing the PI above that required for maintenance of anesthesia. This is termed the **overpressure** technique and may be used to speed the induction of anesthesia, recognizing that sustained delivery of a high PI will result in an anesthetic overdose.

When blood solubility is low, minimal amounts of inhaled anesthetic must be dissolved before equilibration is achieved; therefore, the rate of increase of PA and Pa, and thus onset-of-drug effects such as the induction of anesthesia, are rapid. For example, the inhalation of a constant PI of nitrous oxide, desflurane, or sevoflurane for about 10 minutes results in a PA that is $\geq 80\%$ of the PI (see [Figure 4.3](#)).^{42,43} Use of an overpressure technique with sevoflurane is more readily accepted by patients because this anesthetic is less pungent than desflurane. Indeed, one or more vital capacity breaths of high concentrations of sevoflurane (7% with 66% nitrous oxide) may result in loss of the eyelash reflex.⁴⁴

Associated with the rapid increase in the Pa of nitrous oxide is the absorption of several liters (up to 10 L during the first 10-15 minutes) of this gas, reflecting its common administration at inhaled concentrations of 60% to 70%. This high-volume absorption of nitrous oxide is responsible for several unique effects of nitrous oxide when it is administered in the presence of volatile anesthetics or air-containing cavities (see the sections “[Concentration Effect](#),” “[Second-Gas Effect](#),” and “[Nitrous Oxide Transfer to Closed Gas Spaces](#)”).

Percutaneous loss of inhaled anesthetics occurs but is too small to influence the rate of increase in the PA.⁴⁵ With the possible exception of methoxyflurane, the magnitude of metabolism of inhaled anesthetics is too small to influence the rate of increase of the PA. This lack of effect reflects the large excess of anesthetic molecules administered and the saturation, by anesthetic concentrations of inhaled drugs, of enzymes responsible for anesthetic metabolism.⁴⁶

Blood:gas partition coefficients are altered by individual variations in water, lipid, and protein content and by the hematocrit of whole blood.^{47,48} For example, blood:gas partition coefficients are about 20% less in blood with a hematocrit of 21% compared with blood with a hematocrit of 43%. Presumably, this decreased solubility reflects the decrease in lipid-dissolving sites normally provided by erythrocytes. Conceivably, decreased solubility of volatile anesthetics in anemic blood would manifest as an increased rate of increase in the PA and a more rapid induction of anesthesia. Ingestion of a fatty meal alters the composition of blood, resulting in an approximately 20% increase in the solubility of volatile anesthetics in blood.⁴⁹

The solubility of inhaled anesthetics in blood varies with age ([Figure 4.12](#)).⁵⁰ The blood solubilities of halothane, enflurane, methoxyflurane, and isoflurane are about 18% less in neonates and the elderly compared to young adults. In contrast, the solubility of the less soluble anesthetic sevoflurane (presumably also true for desflurane) is not different in neonates and adults.⁵¹

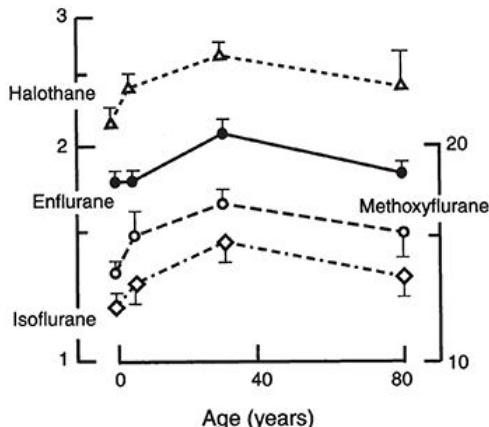


FIGURE 4.12 Blood:gas partition coefficients are 18% less in neonates compared with adults. (Data are mean \pm standard deviation.) Reprinted with permission from Lerman J, Gregory GA, Willis MM, et al. Age and solubility of volatile anesthetics in blood. Anesthesiology. 1984;61(2):139-143. Copyright © 1984 American Society of Anesthesiologists, Inc.

Tissue:Blood Partition Coefficients

Tissue:blood partition coefficients determine uptake of anesthetic into tissues and the time necessary for equilibration of tissues with the Pa. This time for equilibration can be estimated by calculating a time constant (amount of inhaled anesthetic that can be dissolved in the tissue divided by tissue blood flow) for each tissue. One time constant on an exponential curve represents 63% equilibration. Three time constants are equivalent to 95% equilibration. For volatile anesthetics, equilibration between the Pa and P_{BRAIN} depends on the anesthetic's blood solubility and requires 5 to 15 minutes (three time constants). Fat has an enormous capacity to hold anesthetic, and this characteristic, combined with low blood flow to this tissue, prolongs the time required to narrow anesthetic partial pressure differences between arterial blood and fat. For example, equilibration of fat with isoflurane (three time constants) based on this drug's fat:blood partition coefficient and an assumed fat blood flow of 2 to 3 mL per minute per 100 g fat is estimated to be 25 to 46 hours. Fasting before elective operations results in transport of fat to the liver, which could increase anesthetic uptake by this organ and modestly slow the rate of increase in the PA of a volatile anesthetic during induction of anesthesia.⁵²

Oil:Gas Partition Coefficients

Oil:gas partition coefficients parallel anesthetic requirements. For example, an estimated MAC can be calculated as 150 divided by the oil:gas partition coefficient. The constant, 150, is the average value of the product of oil:gas solubility and MAC for several inhaled anesthetics with widely divergent lipid solubilities. Using this constant, the calculated MAC for a theoretical anesthetic with an oil:gas partition coefficient of 100 would be 1.5%.

Nitrous Oxide Transfer to Closed Gas Spaces

As discussed earlier, one downside of using nitrous oxide is that it has the capacity to accumulate in closed spaces where it can cause damage by increasing pressure. The blood:gas partition coefficient of nitrous oxide (0.46) is about 34 times greater than that of nitrogen (0.014). This differential solubility means that nitrous oxide can leave the blood to enter an air-filled cavity 34 times more rapidly than nitrogen can leave the cavity to enter blood. As a result of this preferential transfer of nitrous oxide, the volume or pressure of an air-filled cavity increases. Passage of nitrous oxide into an air-filled cavity surrounded by a compliant wall (intestinal gas, pneumothorax, pulmonary blebs, air bubbles) causes the gas space to expand ([Figure 4.13](#)).⁵³ Conversely, passage of nitrous oxide into an air-filled cavity surrounded by a noncompliant wall (middle ear, cerebral ventricles, supratentorial space) causes an increase in intracavitary pressure.

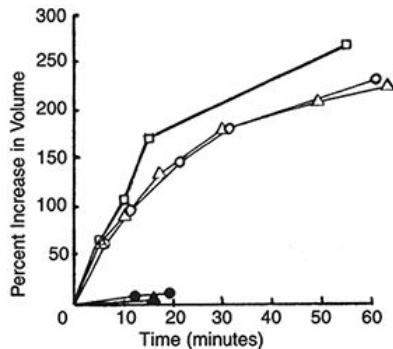


FIGURE 4.13 Inhalation of 75% nitrous oxide rapidly increases the volume of a pneumothorax (open symbols). Inhalation of oxygen (solid symbols) does not alter the volume of the pneumothorax. *Reprinted with permission from Eger EI II, Saidman LJ. Hazards of nitrous oxide anesthesia in bowel obstruction and pneumothorax. Anesthesiology. 1965;26(1):61-66. Copyright © 1965 American Society of Anesthesiologists, Inc.*

The magnitude of volume or pressure increase is influenced by (1) partial pressure of nitrous oxide, (2) blood flow to the air-filled cavity, and (3) duration of nitrous oxide administration. In an animal model, the inhalation of 75% nitrous oxide doubles the volume of a pneumothorax in 10 minutes.⁵³ The finding emphasizes the high blood flow to this area. Likewise, air bubbles (emboli) expand rapidly when exposed to nitrous oxide (Figure 4.14).⁵⁴ Nevertheless, in neurosurgical patients operated on in the sitting position, 50% nitrous oxide has no measurable effect on the incidence or severity of venous air embolism if its administration is discontinued immediately upon Doppler detection of venous air embolism.⁵⁵ In contrast to the rapid expansion of a pneumothorax, the increase in bowel gas volume produced by nitrous oxide is slow but can result in an increase in distention and postoperative pain after a 3-hour surgery.

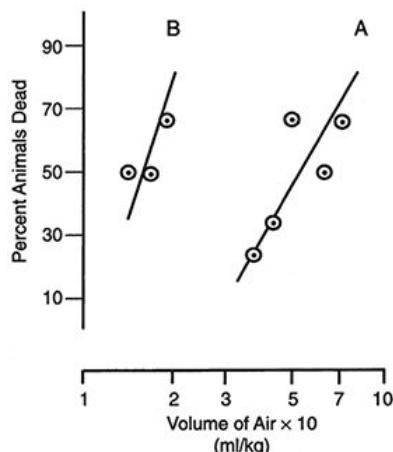


FIGURE 4.14 Nitrous oxide rapidly expands air bubbles as reflected by the volume of injected air necessary to produce 50% mortality in animals breathing nitrous oxide (0.16 mL/kg) (A) compared with animals breathing oxygen (0.55 mL/kg) (B). *Reprinted with permission from Munson ES, Merrick HC. Effect of nitrous oxide on venous air embolism. Anesthesiology. 1966;27(6):783-787. Copyright © 1966 American Society of Anesthesiologists, Inc.*

The middle ear is an air-filled cavity that vents passively via the Eustachian tube when pressure reaches 20 to 30 cm H₂O. Nitrous oxide diffuses into the middle ear more rapidly than nitrogen leaves, and middle ear pressures may increase if Eustachian tube patency is compromised by inflammation or edema. Indeed, tympanic membrane rupture has been attributed to this mechanism after administration of nitrous oxide. Negative middle ear pressures may develop after discontinuation of nitrous oxide, leading to serous otitis.

Nausea and vomiting that may follow general anesthesia may be due to multiple mechanisms, but the role of altered middle ear pressures as a result of nitrous oxide is a consideration.

Intraocular gas bubbles as used for internal retinal tamponade (retinal detachment, macular hole repair, complicated vitrectomy) may persist in the eye for up to 10 weeks following ocular surgery. Administration of nitrous oxide for periods as brief as 1 hour during this time period may result in rapid increases in the volume of intraocular gas within the rigid closed eye that is sufficient to compress the retinal artery with resulting visual loss.⁵⁶

Cardiopulmonary Bypass

Cardiopulmonary bypass produces changes in blood-gas solubility that depend on the constituents of the priming solution and temperature.⁵⁷ Nevertheless, the overall effect of hypothermic cardiopulmonary bypass and a crystalloid prime on blood-gas solubility is only 2%. Volatile anesthetics initiated during cardiopulmonary bypass take longer to equilibrate, whereas the same drugs already present when cardiopulmonary bypass is initiated are diluted, potentially decreasing the depth of anesthesia.

Cardiac Output

Cardiac output (pulmonary blood flow) influences uptake and therefore PA by carrying away either more or less anesthetic from the alveoli. An increased cardiac output results in more rapid uptake, so the rate of increase in the PA and thus the induction of anesthesia are slowed. A decreased cardiac output speeds the rate of increase of the PA because there is less uptake to oppose input.

The effect of cardiac output on the rate of increase in the PA may seem paradoxical. For example, the uptake of more drugs by an increased cardiac output should speed the rate of increase of partial pressures in tissues and thus narrow the A-vD for anesthetics. Indeed, an increase in cardiac output does hasten equilibration of tissue anesthetic partial pressures with the Pa. Nevertheless, the Pa is lower than it would be if cardiac output were normal. Conceptually, a change in cardiac output is analogous to the effect of a change in solubility. For example, doubling cardiac output increases the capacity of blood to hold anesthetic, just as solubility increases the capacity of the same volume of blood.

As with alveolar ventilation, changes in cardiac output most influence the rate of increase of the PA of a soluble anesthetic. Conversely, the rate of increase of the PA of a poorly soluble anesthetic, such as nitrous oxide, is rapid regardless of physiologic deviations of the cardiac output around its normal value. As a result, changes in cardiac output exert little influence on the rate of increase of the PA of nitrous oxide. In contrast, doubling the cardiac output will greatly increase the uptake of soluble anesthetic from alveoli, slowing the rate of increase of the PA. Conversely, a low cardiac output, as with shock, could produce an unexpectedly high PA of a soluble anesthetic.

Volatile anesthetics that depress cardiac output can exert a positive feedback response that contrasts with the negative (protective) feedback response on spontaneous breathing exerted by these drugs. For example, decreases in cardiac output due to an excessive dose of volatile anesthetic results in an increase in the PA, which further increases anesthetic depth and thus cardiac depression. The administration of a volatile anesthetic that depresses cardiac output, plus controlled ventilation of the lungs, results in a situation characterized by unopposed input of anesthetic via alveolar ventilation combined with decreased uptake because of decreased cardiac output. The net effect of this combination of events can be an unexpected, abrupt increase in the PA and an excessive depth of anesthesia.

Distribution of cardiac output will influence the rate of increase of the PA of an anesthetic. For example, increases in cardiac output are not necessarily accompanied by proportional increases in blood flow to all tissues. Preferential perfusion of vessel-rich group tissues when the cardiac output increases results in a more rapid increase in the PA of anesthetic than would occur if the increased cardiac output was distributed equally to all tissues. Indeed, infants have a relatively greater perfusion of vessel-rich group tissues than do adults and, consequently, show a faster rate of increase of the PA toward the PI (see [Figure 4.10](#)).³⁹

Impact of a Shunt

In the absence of an intracardiac or intrapulmonary right-to-left shunt, it is valid to assume that the Pa and Pa_a of inhaled anesthetics are essentially identical. When a right-to-left shunt is present, the diluting effect of the shunted blood on the partial pressure of anesthetic in blood coming from ventilated alveoli results in a decrease in the Pa and a slowing in the induction of anesthesia. Monitoring the end-tidal concentration of anesthetic or carbon dioxide reveals a gradient between the PA and Pa in which the PA underestimates the Pa. A similar mechanism is responsible for the decrease in PaO₂ and the gradient between the PA and Pa in the presence of a right-to-left shunt.

The relative impact of a right-to-left shunt on the rate of increase in the Pa depends on the solubility of the anesthetic. For example, a right-to-left shunt slows the rate of increase of the Pa of a poorly soluble anesthetic more than that of a soluble anesthetic.⁵⁸ This occurs because uptake of a soluble anesthetic offsets dilutional effects of shunted blood on the Pa. Uptake of a poorly soluble drug is minimal, and dilutional effects on the Pa are relatively unopposed. This impact of solubility in the presence of a right-to-left shunt is opposite to that observed with changes in cardiac output and alveolar ventilation. All factors considered, it seems unlikely that a right-to-left shunt alone will alter the speed of induction of anesthesia significantly.

Left-to-right tissue shunts (arteriovenous fistulas, volatile anesthetic-induced increases in cutaneous blood flow) result in delivery to the lungs of blood containing a higher partial pressure of anesthetic than that present in blood that has passed through tissues. As a result, left-to-right shunts offset the dilutional effects of a right-to-left shunt on the Pa. Indeed, the effect of a left-to-right shunt on the rate of increase in the Pa is detectable only if there is a concomitant presence of a right-to-left shunt. Likewise, the effect of a right-to-left shunt on the rate of increase in the PA is maximal in the absence of a left-to-right shunt.

Alveolar-to-Venous Partial Pressure Differences

The A-vD reflects tissue uptake of the inhaled anesthetic. Tissue uptake affects uptake at the lung by controlling the rate of increase of the mixed venous partial pressure of anesthetic. Factors that determine the fraction of anesthetic removed from blood traversing a tissue parallel those factors that determine uptake at the lungs (tissue solubility, tissue blood flow, and arterial-to-tissue partial pressure differences).

Highly perfused tissues (brain, heart, kidneys) in the adult account for <10% of body mass but receive 75% of the cardiac output (**Table 4.4**). As a result of the small mass and high blood flow, these tissues, known as **vessel-rich group tissues**, equilibrate rapidly with the Pa. Indeed, after about three time constants, approximately 75% of the returning venous blood is at the same partial pressure as the PA. For this reason, uptake of a volatile anesthetic is decreased greatly after three time constants (5-15 minutes, depending on the blood solubility of the inhaled anesthetic), as reflected by a narrowing of the inspired-to-alveolar partial pressure difference. Continued uptake of anesthetic after saturation of vessel-rich group tissues reflects principally the entrance of anesthetic into skeletal muscles and fat. Skeletal muscles and fat represent about 70% of the body mass but receive only about 25% of the cardiac output (see **Table 4.4**). As a result of the large tissue mass, sustained tissue uptake of the inhaled anesthetic continues and the effluent venous blood is at a lower partial pressure than the PA. For this reason, the A-vD difference for anesthetic is maintained and uptake from the lungs continues, even after several hours of continuous administration of inhaled anesthetics.

TABLE 4.4

Body tissue composition

	Body mass (% of 70-kg adult)	Blood flow (% of cardiac output)
Vessel-rich group	10	75
Muscle group	50	19
Fat group	20	6
Vessel-poor group	20	<1

The time for equilibration of vessel-rich group tissues is more rapid for neonates and infants than for adults. This difference reflects the greater cardiac output to vessel-rich group tissues in the very young as well

as decreased solubility of anesthetics in the tissues of neonates. Furthermore, skeletal muscle bulk comprises a small fraction of body weight in neonates and infants.

Recovery From Anesthesia

Recovery from anesthesia is depicted by the rate of decrease in the P_{BRAIN} as reflected by the PA (Figure 4.15).^{42,43} The rate of washout of anesthetic from the brain should be rapid because inhaled anesthetics are not highly soluble in brain and the brain receives a large fraction of the cardiac output. Although similarities exist between the rate of induction and recovery, as reflected by changes in the PA of the inhaled anesthetic, there are important differences between the two events. In contrast to induction of anesthesia, which may be accelerated by the concentration effect, it is not possible to speed the decrease in PA by this mechanism (you cannot administer less than zero). Furthermore, at the conclusion of every anesthetic, the concentration of the inhaled anesthetic in tissues depends highly on the solubility of the inhaled drug and the duration of its administration. This contrasts with tissue concentrations of zero at the initiation of induction of anesthesia. The failure of certain tissues to reach equilibrium with the PA of the inhaled anesthetic during maintenance of anesthesia means that the rate of decrease of the PA during recovery from anesthesia will be more rapid than the rate of increase of the PA during induction of anesthesia (see Figures 4.3 and 4.15).^{42,43} Indeed, even after a prolonged anesthetic, skeletal muscles probably, and fat almost certainly, will not have equilibrated with the PA of the inhaled anesthetic. Thus, when the PI of an anesthetic is abruptly decreased to zero at the conclusion of an anesthetic, these tissues initially cannot contribute to the transfer of drug back to blood for delivery to the liver for metabolism or to the lungs for exhalation. As long as gradients exist between the Pa and tissues, the tissues will continue to take up anesthetic. Thus, during recovery from anesthesia, the continued passage of anesthetic from blood to tissues, such as fat, acts to speed the rate of decrease in the PA of that anesthetic. Continued tissue uptake of anesthetic will depend on the solubility of the inhaled anesthetic and the duration of anesthesia, with the impact being most important with soluble anesthetics.⁵⁹ For example, time to recovery is prolonged in proportion to the duration of anesthesia for soluble anesthetics (halothane and isoflurane), whereas the impact of duration of administration on time to recovery is minimal with poorly soluble anesthetics (sevoflurane and desflurane) (Figure 4.16).¹ The importance of these differences depend on the context of the administration, thus called context-sensitive half-time.

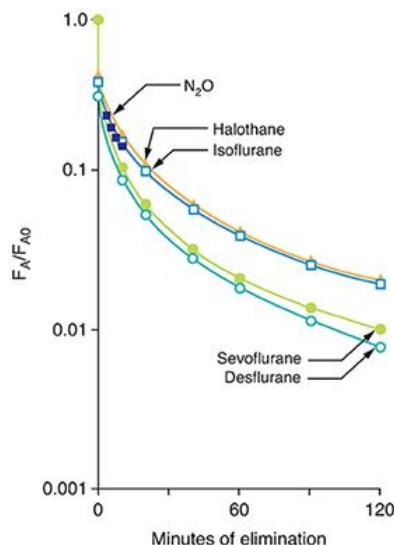


FIGURE 4.15 Elimination of inhaled anesthetics is defined as the ratio of the end-tidal anesthetic concentration (F_A) to the F_A immediately before the beginning of elimination (F_{AO}). The rate of decrease (awakening from anesthesia) in the F_A/F_{AO} is most rapid with the anesthetics that are least soluble in blood (nitrous oxide [N_2O], desflurane, sevoflurane). *Reprinted with permission from Yasuda N, Lockhart SH, Eger*

EI, et al. Comparison of kinetics of sevoflurane and isoflurane in humans. Anesth Analg. 1991;72(3):316-324. Copyright © 1991 International Anesthesia Research Society.

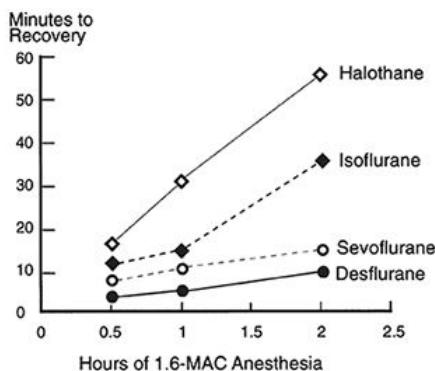


FIGURE 4.16 An increase in the duration of anesthesia during a constant dose of anesthetic (1.6 MAC) is associated with increases in the time to recovery (motor coordination in an animal model), with the greatest increases occurring with the most blood-soluble anesthetics. *Derived from Eger EI. Desflurane (Suprane): A Compendium and Reference. Nutley, NJ: Anaquest; 1993:1-119.*

Anesthetic that has been absorbed into the components of the anesthetic breathing system will pass from the components back into the gases of the breathing circuit at the conclusion of anesthesia and retard the rate of decrease in the PA of the anesthetic. Likewise, exhaled gases of the patient contain anesthetic that will be rebreathed unless fresh gas flow rates are increased (at least 5 L per minute of oxygen) at the conclusion of anesthesia.

Context-Sensitive Half-Time

The pharmacokinetics of the elimination of inhaled anesthetics depends on the length of administration and the blood-gas solubility of the inhaled anesthetic. As with injected anesthetics, it is possible to use computer simulations to determine context-sensitive half-times for volatile anesthetics.⁶⁰ For example, [Figure 4.17](#) shows the times for decrements in the vessel-rich group of 80%, 88%, 90%, 92%, and 95% for isoflurane, sevoflurane, and desflurane. The figures provide mathematical quantification of two obvious clinical observations. First, recovery is always fastest for desflurane, the most insoluble anesthetic, and always slowest for isoflurane, the most soluble anesthetic. Second, the greater the percentage decrease required for anesthesia, the longer duration required for recovery from anesthetic.

However, [Figure 4.17](#) provides more detailed insight as well. A typical anesthetic might require 90% decrease in inhaled concentration after maintaining 1 MAC. This is the decrement in [Figure 4.17C](#). If the anesthetic is about 30 minutes' duration, then there will be no difference in recovery time between desflurane, sevoflurane, or isoflurane. This makes it clear why the argument that desflurane has an advantage in short procedures is nonsense. Any of the three volatile anesthetics will provide a faster recovery. Indeed, one has to get to an anesthetic of about 2 hours to see an appreciable benefit of desflurane over sevoflurane. (As discussed in the section that follows, one has to weigh the benefit of a few minutes faster recovery against the consequential greenhouse gas contribution of desflurane.) [Figure 4.17C](#) provides guidance on how to administer sevoflurane and get a rapid recovery: Turn it off early! If the anesthetic is 3 to 4 hours' duration, then about 30 minutes before the end of the case, turn off sevoflurane and replace it with 70% nitrous oxide. This will give the sevoflurane adequate time to decrease 90%, ensuring rapid recovery once the nitrous is discontinued at the end of surgery.

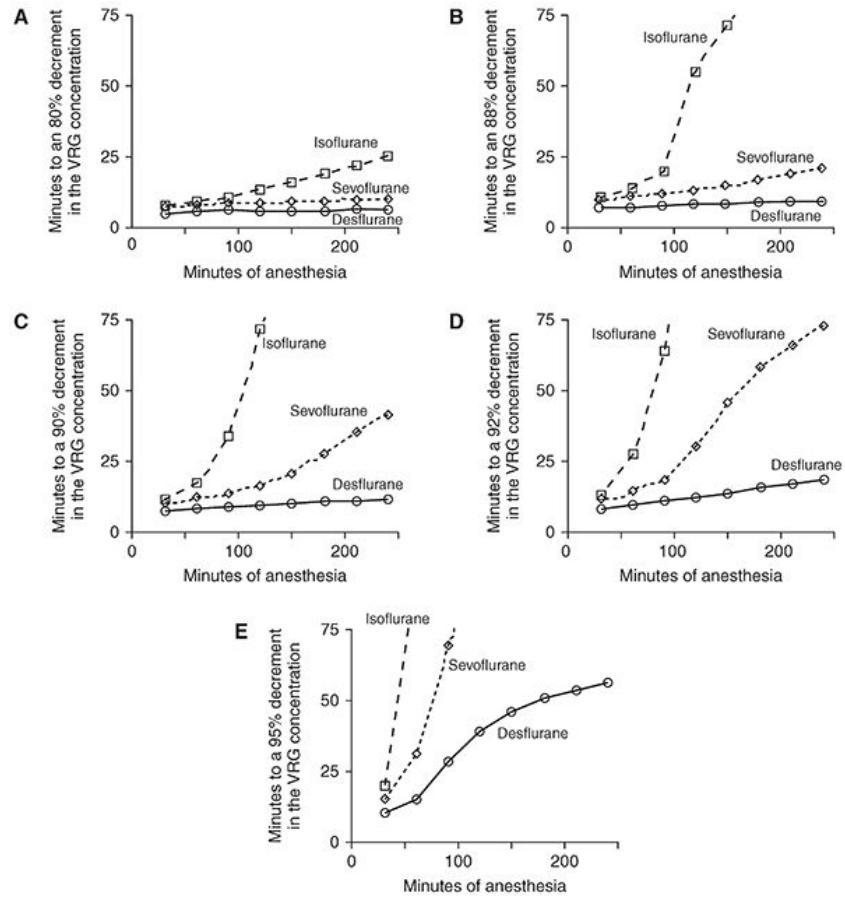


FIGURE 4.17 Graphs A, B, C, D, and E show the times required for decrements in the vessel-rich group (VRG) concentration of inhaled anesthetic of 80%, 88%, 90%, 92%, and 95%, respectively. As can be seen by comparing the individual graphs, the decrement times can become exceptionally long if a large decrement in anesthetic concentration is required to awaken from anesthesia. This quantifies the obvious clinical observation that rapid emergence is facilitated by administering the lowest concentration of an inhaled anesthetic necessary to maintain unconsciousness. *Reprinted with permission from Eger EI II, Shafer SL. Tutorial: context-sensitive decrement times for inhaled anesthetics. Anesth Analg. 2005;101(3):688-696. Copyright © 2005 International Anesthesia Research Society.*

In this regard, the time needed for a 50% decrease in anesthetic concentration of enflurane, isoflurane, desflurane, and sevoflurane is <5 minutes and does not increase significantly with increasing duration of anesthesia.⁶¹ Presumably, this is a reflection of the initial phase of elimination, which is primarily a function of alveolar ventilation. Determination of other decrement times (80% and 90%) reveals differences between various inhaled anesthetics. For example, the 80% decrement times of desflurane and sevoflurane are <8 minutes and do not increase significantly with the duration of anesthesia, whereas 80% decrement times for enflurane and isoflurane increase significantly after about 60 minutes, reaching plateaus of approximately 30 to 35 minutes. The 90% decrement time of desflurane increases slightly from 5 minutes after 30 minutes of anesthesia to 14 minutes after 6 hours of anesthesia, which is significantly less than sevoflurane (65 minutes), isoflurane (86 minutes), and enflurane (100 minutes) after 6 hours of administration. Based on the simulated context-sensitive half-times and assuming that MAC-awake is 0.5 MAC, there would be little difference in recovery time among these volatile anesthetics when a pure inhalation anesthetic technique is used. The major differences in the rates at which desflurane, sevoflurane, isoflurane, and enflurane are eliminated occur in the final 20% of the elimination process.

Diffusion Hypoxia

Diffusion hypoxia occurs when inhalation of nitrous oxide is discontinued abruptly, leading to a reversal of partial pressure gradients such that nitrous oxide leaves the blood to enter alveoli.⁶² This initial high-volume outpouring of nitrous oxide from the blood into the alveoli can so dilute the PAO_2 that the PaO_2 decreases. In addition to dilution of the PAO_2 by nitrous oxide, there is also dilution of the PACO_2 , which decreases the stimulus to breathe.⁶³ This decreased stimulus to breathe exaggerates the impact on PaO_2 of the outpouring of nitrous oxide into the alveoli. Outpouring of nitrous oxide into alveoli is greatest during the first 1 to 5 minutes after its discontinuation at the conclusion of anesthesia. Thus, it is common practice to fill the lungs with oxygen at the end of anesthesia to ensure that arterial hypoxemia will not occur as a result of dilution of the PAO_2 by nitrous oxide.

Pharmacodynamics of Inhaled Anesthetics

Minimal Alveolar Concentration

The MAC of an inhaled anesthetic is defined as that concentration at 1 atm that prevents skeletal muscle movement in response to a supramaximal painful stimulus (surgical skin incision) in 50% of patients.⁶⁴ The MAC is anesthetic 50% effective dose (ED_{50}). Immobility produced by inhaled anesthetics as measured by MAC is mediated principally by effects of these drugs on the spinal cord and only a minor component of immobility results from cerebral effects.⁶⁵ For example, in animals, MAC for isoflurane is 1.2% when delivered to the intact animal but delivery of inhaled anesthetic only to the brain results in isoflurane MAC increasing to nearly 3%.⁶⁶ Further evidence that MAC reflects effects of the inhaled anesthetics at the spinal cord is the observation that decerebration does not change MAC (Figure 4.18).⁶⁷

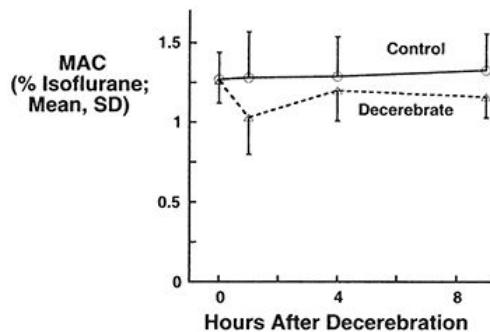


FIGURE 4.18 Decerebration does not change the minimum alveolar anesthetic concentration of isoflurane in rats confirming that the effects of volatile anesthetics on the spinal cord determine minimal alveolar concentration (MAC). Abbreviation: SD, standard deviation. Reprinted with permission from Rampil IJ, Mason P, Singh H. Anesthetic potency (MAC) is independent of forebrain structures in the rat. *Anesthesiology*. 1993;78(4):707-712. Copyright © 1993 American Society of Anesthesiologists, Inc.

The MAC is among the most useful concepts in anesthetic pharmacology as it establishes a common measure of potency (partial pressure at steady state) for inhaled anesthetics. This concept is used to provide uniformity in dosages of inhaled anesthetics, to establish relative amounts of inhaled anesthetics to reach specific endpoints (MAC-aware), and to guide the search for mechanisms responsible for mechanisms of anesthetic action.⁶⁸ A unique feature of MAC is its consistency varying only 10% to 15% among individuals. This small degree of pharmacodynamic variability for inhaled anesthetics is unique in pharmacology. The use of equally potent doses (comparable MAC) of inhaled anesthetics is mandatory for comparing effects of these drugs not only at the spinal cord but also at all other organs (Table 4.5). For example, similar MACs of inhaled anesthetics produce equivalent depression of the spinal cord, whereas effects on cardiopulmonary parameters may be different for each drug (see Chapter 2). This emphasizes that MAC represents only one point on the dose-response curve of effects produced by inhaled anesthetics and that these dose-response curves are not parallel. It is remarkable though that MAC-aware, the concentration of anesthetic that prevents

consciousness in 50% of persons, is reliably about half of MAC and that MAC-memory, the concentration of anesthetic that is associated with amnesia in 50% of patients, is significantly less than MAC-aware. If this were not the case, an ED₅₀ would not be satisfactory end point for clinical anesthesia! A surgeon may tolerate 50% of his or her patients moving but having 50% of patients have awareness under anesthesia would clearly not be acceptable.

TABLE 4.5

Comparative minimal alveolar concentration (MAC) of inhaled anesthetics

	MAC (% , 30-55 years old at 37°C, PB 760 mm Hg)
Nitrous oxide ^a	104
Halothane	0.75
Enflurane	1.63
Isoflurane	1.17
Desflurane	6.6
Sevoflurane	1.80
Xenon	63-71

Abbreviation: P_B, brain partial pressure.

^aDetermined in a hyperbaric chamber in males 21 to 55 years old.

Factors That Alter Minimal Alveolar Concentration

Inhalation anesthetic requirements are remarkably uniform in humans, mainly being affected by age and body temperature. The MAC allows a quantitative analysis of the effect, if any, of various physiologic and pharmacologic factors on anesthetic requirements ([Table 4.6](#)).⁵⁹⁻⁸¹ For example, increasing age results in a progressive decrease in MAC of about 6% per decade that is similar for all inhaled anesthetics ([Figures 4.19](#) and [4.20](#)).^{82,83} The MAC is decreased nearly 30% during pregnancy and in the early postpartum period, returning to normal values in 12 to 72 hours.^{84,85} However, the incidence of postoperative awareness is higher after cesarean section than most surgeries aside from cardiothoracic surgery. The MAC, the concentration of anesthetic required to prevent movement, is mediated predominantly by a spinal reflex.^{66,67} Although MAC is reduced in parturients, there is evidence that the concentration response in the brain is not changed. For example, the dose of volatile anesthetic required to induce the electroencephalogram (EEG) changes expected with hypnosis are not changed in pregnancy.⁸⁶ Anesthetic concentrations required to reduce awareness reflect those in the brain.

TABLE 4.6

Impact of physiologic and pharmacologic factors on minimal alveolar concentration (MAC)

Increases in MAC

Hyperthermia

Excess pheomelanin production (red hair)

Drug-induced increases in central nervous system catecholamine levels (cocaine, methamphetamine, amphetamine)

Cyclosporine

Hypernatremia

Decreases in MAC

Hypothermia

Increasing age

Preoperative medication

Drug-induced decreases in central nervous system catecholamine levels

α_2 Agonists
Acute alcohol ingestion
Pregnancy
Postpartum (returns to normal in 24-72 hours)
Lidocaine
Neuraxial opioids
$\text{PaO}_2 < 38 \text{ mm Hg}$
Mean blood pressure $< 40 \text{ mm Hg}$
Cardiopulmonary bypass
Hyponatremia
No change in MAC
Anesthetic metabolism
Chronic alcohol abuse
Sex
Duration of anesthesia
$\text{Paco}_2 15\text{--}95 \text{ mm Hg}$
$\text{PaO}_2 > 38 \text{ mm Hg}$
Blood pressure $> 40 \text{ mm Hg}$
Hyperkalemia or hypokalemia
Thyroid gland dysfunction

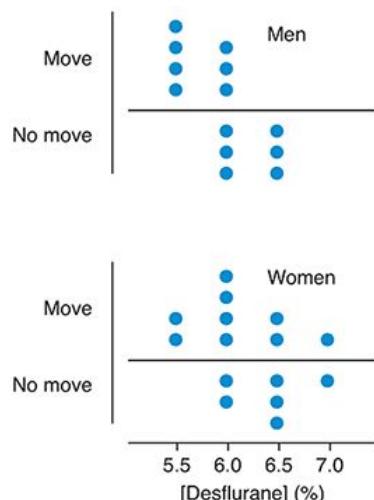


FIGURE 4.19 End-tidal concentrations of desflurane were tested for “move” or “no move” in men and women. Minimal alveolar concentration for desflurane in men was 6.0% to 0.3%, and in women, it was 6.2% to 0.4% ($P = .31$ [mean – SD]). Reprinted with permission from Wadhwa A, Durrani J, Sengupta P, et al. Women have the same desflurane minimum alveolar concentration as men: a prospective study. Anesthesiology. 2003;99(5):1062-1065. Copyright © 2003 American Society of Anesthesiologists, Inc.

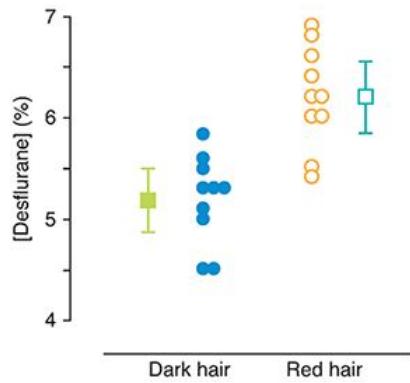


FIGURE 4.20 Anesthetic requirements for individual participants (circles) with group means (squares). The desflurane requirement in redheads (6.2%) was significantly greater than in dark-haired women (5.2%).
Reprinted with permission from Liem EB, Lin C-M, Suleman M-I, et al. Anesthetic requirement is increased in redheads. *Anesthesiology*. 2004;101(2):279-283. Copyright © 2004 American Society of Anesthesiologists, Inc.

Gender does not influence MAC (see [Figure 4.19](#)).^{87,88} The MAC is increased in women with natural red hair, presumably reflecting mutations of the melanocortin-1 receptor gene and increased pheomelanin concentrations (see [Figure 4.20](#)).⁸⁹ Although most reports describe MAC as independent of the duration of anesthesia, there is evidence that MAC for isoflurane decreases during the administration of anesthesia and the performance of surgery ([Figure 4.21](#)).⁹⁰ The effect of cardiopulmonary bypass on MAC is uncertain, with some studies showing a decrease, whereas others fail to demonstrate any change.⁵⁷ Despite prolongation of sleeping times in animals, cyclosporine increases rather than decreases isoflurane MAC.⁹¹ A MAC is defined by the response to a surgical incision, which is considered to be a supramaximal stimulus. The MAC values may vary with the type of stimulus; tetanic stimulation and trapezius squeeze are considered noninvasive stimulation patterns that are relatively equivalent to surgical skin incision, although in contrast to skin incision, these events can be repeated ([Figure 4.22](#)).⁹² Tracheal intubation requires the highest MAC to prevent skeletal muscle responses and may represent a true supramaximal stimulation (see [Figure 4.22](#)).⁹²

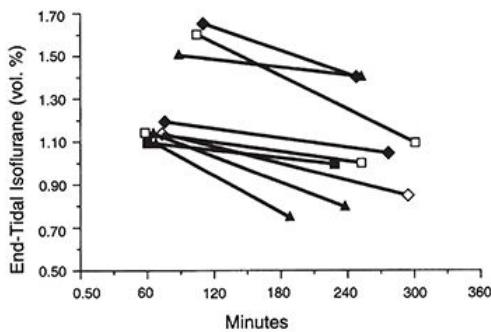


FIGURE 4.21 Preoperative (60 minutes) and postoperative (180–300 minutes) individual minimal alveolar concentration (MAC) determinations using continuous electrical stimulation (MAC tetanus). Each line represents an individual patient. Reprinted with permission from Petersen-Felix S, Zbinden AM, Fischer M, et al. Isoflurane minimum alveolar concentration decreases during anesthesia and surgery. *Anesthesiology*. 1993;79(5):959-965. Copyright © 1993 American Society of Anesthesiologists, Inc.

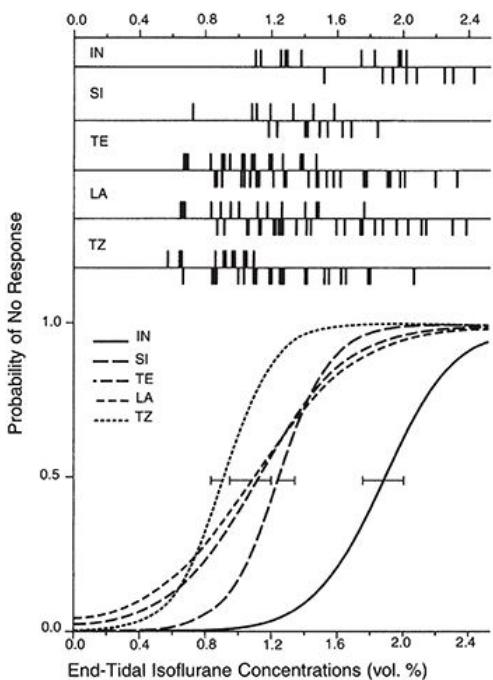


FIGURE 4.22 Responses (movement [horizontal line above] or no movement [horizontal line below]) to preoperative stimulation represented by tracheal intubation (IN), skin incision (SI), response to a continuous (tetanus) electrical stimulation (TE), direct laryngoscopy (LA), and trapezius muscle squeeze (TZ). The probability of response versus end-tidal isoflurane concentration is plotted. *Reprinted with permission from Zbinden AM, Maggiorini M, Peterson-Felix S, et al. Anesthetic depth defined using multiple noxious stimuli during isoflurane/oxygen anesthesia. I. Motor reactions. Anesthesiology. 1994;80(2):253-260. Copyright © 1994 American Society of Anesthesiologists, Inc.*

The MAC values for inhaled anesthetics are additive.⁹³ For example, 0.5 MAC of nitrous oxide plus 0.5 MAC isoflurane has the same effect at the brain as does a 1 MAC of either anesthetic alone. The strict additivity of the interactions among inhaled anesthetics implies either a common site of action or that anesthetic action occurs with only a small fraction of the binding sites occupied.⁹⁴

Opioids synergistically decrease anesthetic requirements for volatile anesthetics. For example, 25 minutes after the administration of fentanyl, 3 or 6 µg/kg intravenously (IV), MAC for desflurane is decreased 48% and 68%, respectively.⁹⁵ Similar decreases in isoflurane MAC are also produced by these doses of fentanyl.⁹⁶ The MAC values for volatile anesthetics and ED₅₀ concentrations for intravenous anesthetics are for the most part not additive but synergistic. As a general rule, drugs that act on different receptors or by different mechanisms are typically not additive.^{94,97} Dose-response curves for inhaled anesthetics, although not parallel, are all steep. This is emphasized by the fact that a 1 MAC dose prevents skeletal muscle movement in response to a painful stimulus in 50% of patients, whereas a modest increase to about 1.3 MAC prevents movement in at least 95% of patients.

Mechanisms of Anesthetic Action

Meyer-Overton Theory (Critical Volume Hypothesis)

The mechanism of volatile anesthetic action is one of the great unsolved mysteries of our time. We know quite exactly how most systemically administered drugs work, often down to the specific molecular binding sites. Volatile anesthetics have been a hard nut to crack. Various theories have held precedence over the years, but no consensus has been reached that explains the ability of volatile anesthetics to induce unconsciousness.

Correlation between the lipid solubility of inhaled anesthetics (oil:gas partition coefficient) and anesthetic potency has historically been presumed to be evidence that inhaled anesthetics act by disrupting

the structure or dynamic properties of the lipid portions of nerve membranes. For example, when a sufficient number of molecules dissolve (critical concentration) in crucial hydrophobic sites such as lipid cell membranes, there is distortion of channels necessary for ion flux and the subsequent development of action potentials needed for synaptic transmission. Likewise, changes in the lipid matrix produced by dissolved anesthetic molecules could alter the function of proteins in cell membranes, thus decreasing sodium conductance. Evidence supporting distortion of sodium channels by dissolved anesthetic molecules is the observation that high pressures (40–100 atm) partially antagonize the action of inhaled anesthetics (pressure reversal), presumably by returning (compressing) lipid membranes and their sodium channels to their “awake” contour.⁹⁸

The most compelling evidence against the Meyer-Overton theory of anesthesia is the fact that effects of inhaled anesthetics on the fluidity of lipid bilayers is implausibly small and can generally be mimicked by temperature changes of 1°C.⁹⁹ Furthermore, not all lipid-soluble drugs are anesthetics, and, in fact, some are convulsants. For example, the observation that, among *n*-alcohols, dodecanol is anesthetic and decanol is not (for *n*-alkanes the cutoff is after octane) suggests that anesthetic binding to protein pockets or clefts and not lipid membranes is important in the mechanism of anesthesia. Based on these negative observations, lipid theories have been refined to postulate that specialized domains in membranes (boundary membranes surrounding proteins) are not only particularly sensitive to anesthetics but also are critical to membrane function. Indeed, either binding to proteins or dissolving in lipids could account for the Meyer-Overton correlation.

Stereoselectivity

The effects of inhaled anesthetics on ion channels responsible for neuronal action are readily demonstrated (**Figure 4.23**).⁹⁹ The most definitive evidence that general anesthetics act by binding directly to proteins and not a lipid bilayer comes from observations of stereoselectivity.¹⁰⁰ Inhalation anesthetics exist as isomers, and isoflurane has been shown to act stereoselectively on neuronal channels, with the levoisomer being more potent than the dextroisomer in enhancing potassium conductance in neurons¹⁰¹ and in with respect to the loss of righting reflex in animals.¹⁰² The relevance to anesthetic mechanisms of the differing effects of enantiomers of volatile anesthetics on *in vitro* nerve conduction would be supported by parallel changes in MAC in the intact animal. Indeed, in rats, MAC for the levoisomer of isoflurane was 60% more potent than the dextroisomer.¹⁰³ In contrast, others have not found a significant difference in the effects of the enantiomers of isoflurane and desflurane on anesthetic effects in animals.¹⁰⁴ Receptor specificity is also suggested by conversion of an anesthetic to a nonanesthetic by increasing the molecular volume, despite corresponding increases in lipid solubility. Nevertheless, there is evidence that molecular shape (bulkiness) and size provide limited insight into the structure of the anesthetic site of action.¹⁰⁵

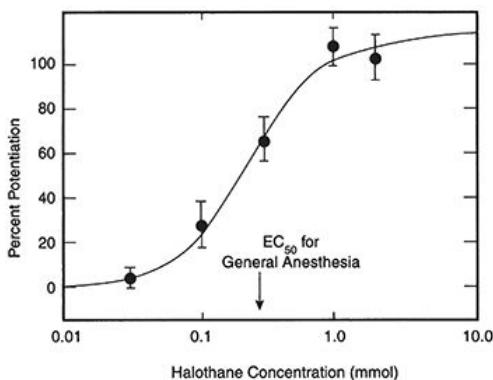


FIGURE 4.23 Clinically relevant concentrations of halothane (0.23 mmol) is near the median effective concentration [EC_{50}] for anesthesia) potentiate responses to low levels of γ -aminobutyric acid in dissociated rat brain neurons. *Reprinted by permission from Nature: Franks NP, Lieb WR. Molecular and cellular*

mechanisms of general anaesthesia. Nature. 1994;367(6464):607-614. Copyright © 1994 Nature Publishing Group.

Potential Mediators of Anesthetic Action

Ionotropic and Metabotropic Receptors

Neurotransmitters signal through two families of receptors designated as ionotropic and metabotropic. Ionotropic receptors are also known as **ligand-gated ion channels** because the neurotransmitter binds directly to ion channel proteins and this interaction causes opening (gating) of the ion channels allowing transmission of specific ions resulting in changes in membrane potential. Ionotropic receptors are often composed of several subunits. Indeed the γ -aminobutyric acid receptor type A (GABA_A) and nicotinic acetylcholine receptors are constructed from large families of evolutionarily related subunits that come together to make pleomorphic receptors. In contrast, metabotropic receptors are usually monomeric receptors consisting of seven transmembrane segments. Binding of neurotransmitters (acetylcholine) to metabotropic receptors causes activation of guanosine triphosphate binding proteins (G proteins) associated with the receptors, and these G proteins act as second messengers to activate other signaling molecules such as protein kinases or potassium or calcium channels.⁶⁵

Inhaled anesthetics do not seem to stimulate the release of endogenous opioids and do not suppress ventilatory responses to surgical stimulation at concentrations that suppress movement. The fact that small doses of opioids decrease MAC reflects their ability to provide an effect (analgesia) that is not present with inhaled anesthetics alone.

Inhibitory Ligand-Gated and Voltage-Gated Channels (Glycine and GABA_A Receptors)

Glycine receptors are major mediators of inhibitory neurotransmission in the spinal cord and may mediate part of the immobility produced by inhaled anesthetics.¹⁰⁶ Their spinal localization and potentiation by volatile anesthetics at clinical concentrations is consistent with their being a target for mediating immobility as defined by MAC.

Although β_3 -subunit-containing GABA_A receptors mediate hypnosis and part of the immobility produced by injected anesthetics (propofol, etomidate),¹⁰⁷ there is evidence that GABA_A receptors do not mediate immobility produced by inhaled anesthetics. In this regard, although GABA_A receptors are potentiated at MACs of all clinically used volatile anesthetics, their enhancement of GABA_A receptor activation minimally influences MAC.¹⁰⁸

Glutamate (NMDA, AMPA, and Kainate Receptors)

Inhaled anesthetics decrease excitatory neurotransmission in the CNS. Glutamate is the principal excitatory neurotransmitter in the mammalian CNS. Glutamate receptors include G protein-coupled receptors and the ligand-gated receptors (NMDA, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid [AMPA], and kainate). The NMDA receptors may mediate some important behavioral effects of inhaled anesthetics. Volatile anesthetics separate into two different classes in terms of their efficacy for NMDA blockade. At 1 MAC, different volatile anesthetics inhibit NMDA receptors by between 14% (sevoflurane) and 39% (Xenon) with those anesthetics having cation-p interactions having the greatest NMDA blockade.¹⁰⁹

Two-Pore Potassium Channels

Two-pore potassium channels are intrinsic membrane receptor/ion channels that normally act to maintain the cell's resting potential and responds to internal stimuli such as a change in pH. Several members of this family have been found to be sensitive to volatile anesthetics at clinically used concentrations. The TREK and TASK channel activity is potentiated by volatile anesthetics in an agent-specific manner.¹¹⁰ The TASK-3 receptors are anesthetic-sensitive receptors that play a role in maintaining theta oscillations in the EEG that are associated with anesthesia and the duration of natural deep sleep.^{111,112} Anesthetic interaction with TASK channels may contribute to anesthetic induced neuroprotective effects in ischemia-reperfusion injury.¹¹³

Voltage-Gated Sodium Channels

It is now clear that there are many subtypes of sodium channels. Although sodium channels that mediate axonal conduction are not significantly effected at MACs of volatile anesthetics, those that modulate the release of neurotransmitter may be more sensitive to anesthetics. There is evidence that by interacting with specific subtypes of sodium channel that are expressed at the presynaptic junction, these drugs can inhibit the release of neurotransmitters, particularly glutamate.¹¹⁴ Indeed, intravenous administration of lidocaine, which is a nonspecific sodium channel blocker, decreases MAC.

Hyperpolarization-Activated Cyclic Nucleotide–Gated Channels

Hyperpolarization-activated cyclic nucleotide–gated channels are voltage-gated ion channels that are expressed throughout the body but are particularly important in regulating rhythmogenicity in heart and brain. There is some suggestion that halothane may affect hyperpolarization-activated cyclic nucleotide–gated channels in motor neurons to induce anesthetic immobility.¹¹⁵

Mechanism of Immobility

The MAC is based on the characteristic ability of inhaled drugs to produce immobility by virtue of actions of these drugs principally on the spinal cord rather than on higher centers.⁶⁵ The observation that immobility during noxious stimulation does not correlate with electroencephalographic activity reflects the fact that cortical electrical activity does not control motor responses to noxious stimulation. Effects of inhaled anesthetics on the spinal cord leading to immobility are diverse. In this regard, inhaled anesthetics depress excitatory AMPA and NMDA receptor–mediated currents by actions independent of inhibitory GABA_A and glycine receptor–mediated currents. Actions on two-pore potassium channels may also be important in producing immobility. Conversely, nicotinic acetylcholine receptors do not seem to exert a significant role in anesthetic-induced immobility at the spinal cord level.¹¹⁶ Likewise, although opioids and stimulation of α₂-adrenergic receptors (clonidine) decrease MAC, it is unlikely that immobility produced by inhaled anesthetics is due to activation of these receptors.⁸⁷ Inhaled anesthetics do not act via opioid receptors. Overall, no inhaled anesthetic action on a single group of receptors yet described can explain immobility, and immobility as a result of concurrent actions on many receptors is unlikely.^{65,117}

Mechanism of Anesthesia-Induced Unconsciousness

A comprehensive explanation of the mechanism by which volatile anesthetics cause loss of consciousness (suppression of awareness) is not known.¹¹⁸ Hypnosis is typically studied in animal models as loss of righting reflex. In human studies, it can be measured as loss of response to command, and in the presence of neuromuscular blockers, the spared arm technique uses a tourniquet to block muscle relaxant access to an arm, which is then used to indicate consciousness. Subtle differences in the clinical effects of inhaled anesthetics may be attributed to distinct actions on a number of critical molecular targets. There is evidence that loss of consciousness (hypnosis), amnesia, and the response to skin incision (immobility as defined by MAC) are not a single continuum of increasing anesthetic depth but rather separate phenomena.^{119,120} Combining these two observations, it has been proposed that general anesthesia is a process requiring a state of unconsciousness of the brain (produced by volatile or injected anesthetics) plus immobility in response to a noxious stimulus (surgical skin incision) that is mediated by the action of volatile anesthetics on the spinal cord administered at concentrations equivalent to MAC for that drug.

It has been proposed that clinical anesthesia is a hierarchical process in which afferent sensory impulses are diminished by some drugs (opioids, regional anesthesia, ketamine) while the central activating systems are depressed by another mechanism and sometimes other drugs (benzodiazepines, barbiturates, propofol, etomidate, ketamine, and volatile anesthetics) and motor reflexes are depressed by yet another mechanism (volatile anesthetics, propofol, etomidate, barbiturates). According to the definition of MAC, only agents that depress motor reflexes in addition to the other actions can be properly considered general anesthetics, but many agents are able to provide one or the other behavioral outcome and can be used as part of a general anesthetic regimen. Volatile anesthetics have been called **total anesthetics** because they can be used as a

single agent to provide general anesthesia. It was long assumed that they decreased pain transmission, but after more thorough consideration, it appears that volatile anesthetics have a biphasic dose response for nociceptive influences such that they are increased at very low volatile anesthetic concentrations (about 10% MAC) and they diminish thereafter.¹²¹ The pronociceptive activity of volatile anesthetics can be attributed to inhibition of heteromeric nicotinic receptors that is complete at very low concentrations around 1 MAC.¹²² This mechanism has been shown to impact emergence from isoflurane but not propofol anesthetics in humans.¹²³

Presynaptic inhibition of neurotransmitter release may explain how certain inhaled anesthetics can inhibit synaptic transmission. Many mechanisms have been proposed for the inhibition of neurotransmitter release by inhaled anesthetics. The mechanism by which anesthetics act to inhibit neurotransmitter release might reflect actions at ion channels that regulate the probability of neurotransmitter release or could act on the machinery of release itself. Recent evidence in rodents supports this view.¹²⁴ As mentioned earlier, halogenated volatile anesthetics inhibit some types of sodium channels in native neurons and in heterologous expression systems.¹²⁵ Although sodium channels can presynaptically modulate the release of both glutamate and GABA, their effect on the release of glutamate is greater than on the release of GABA.¹²⁶ There is recent evidence that isoflurane inhibits presynaptic neurotransmitter release inhibiting both the machinery required for neurotransmitter release.

Comparative Pharmacology of Gaseous Anesthetic Drugs

Inhaled anesthetics evoke different pharmacologic effects at comparable percentages of MACs, emphasizing that dose-response curves for these drugs are not necessarily parallel. Measurements obtained from normothermic volunteers exposed to equal potent concentrations of inhaled anesthetics during controlled ventilation of the lungs to maintain normocapnia have provided the basis of comparison for pharmacologic effects of these drugs on various organ systems.¹²⁷ In this regard, it is important to recognize that surgically stimulated patients who have other confounding variables may respond differently than healthy volunteers (**Table 4.7**).

TABLE 4.7

Variables that influence pharmacologic effects of inhaled anesthetics

Anesthetic concentration
Rate of increase in anesthetic concentration
Spontaneous versus controlled ventilation
Variations from normocapnia
Surgical stimulation
Patient age
Coexisting disease
Concomitant drug therapy
Intravascular fluid volume
Preoperative medication
Injected drugs to induce and/or maintain anesthesia or skeletal muscle relaxation
Alterations in body temperature

Desflurane and sevoflurane provide one specific advantage over other currently available potent inhaled anesthetics.⁴ Their lower blood and tissue solubility permit more precise control over the induction of anesthesia and a more rapid recovery when the drug is discontinued. Most of the other properties of these new volatile anesthetics resemble their predecessors, especially at concentrations of ≤ 1 MAC.

Central Nervous System Effects

Mental impairment is not detectable in volunteers breathing 1,600 ppm (0.16%) nitrous oxide or 16 ppm (0.0016%) halothane.¹²⁸ It is therefore unlikely that impairment of mental function in the personnel who work in the operating room using modern anesthetic scavenging techniques can result from inhaling trace concentrations of anesthetics. Reaction times do not increase significantly until 10% to 20% nitrous oxide is inhaled.¹²⁹

Cerebral metabolic oxygen requirements are decreased in parallel with drug-induced decreases in cerebral activity. Drug-induced increases in CBF may increase intracranial pressure (ICP) in patients with space-occupying lesions. The effects of desflurane and sevoflurane on the CNS do not differentiate these inhaled anesthetics from the older inhaled drugs.

Electroencephalogram

Volatile anesthetics in concentrations of <0.4 MAC similarly increase the frequency and voltage on the EEG. This enhancement is representative of the “excitement stage” of anesthesia. At about 0.4 MAC, there is an abrupt shift of high-voltage activity from posterior to anterior portions of the brain.¹³⁰ Cerebral metabolic oxygen requirements also begin to decrease abruptly at about 0.4 MAC. It is likely that these changes reflect a transition from wakefulness to unconsciousness. Furthermore, amnesia probably occurs at this dose of volatile anesthetic. As the dose of volatile anesthetic approaches 1 MAC, the frequency on the EEG decreases and maximum voltage occurs. During administration of isoflurane, burst suppression appears on the EEG at about 1.5 MAC, and at 2 MAC, electrical silence predominates.¹³¹ Electrical silence does not occur with enflurane, and only unacceptably high concentrations of halothane (>3.5 MAC) produce this effect. The effects of nitrous oxide on the EEG are similar to those produced by volatile anesthetics. Slower frequency and higher voltage develop on the EEG as the dose of nitrous oxide is increased or when nitrous oxide is added to a volatile anesthetic to provide a greater total MAC.

Desflurane and sevoflurane cause dose-related changes in the EEG similar to those that occur with isoflurane.⁴ With desflurane, the EEG progresses from an initial increase in frequency and lowering of voltage at low anesthetic concentrations to increased voltage at anesthetizing concentrations. Higher concentrations of desflurane produce decreasing voltage and increasing periods of electrical silence with an isoelectric EEG at 1.5 to 2.0 MAC. The addition of nitrous oxide to a given level of anesthesia with desflurane causes little or no change in the EEG.

Seizure Activity

Enflurane can produce fast frequency and high voltage on the EEG that often progresses to spike wave activity that is indistinguishable from changes that accompany a seizure. This EEG activity may be accompanied by tonic-clonic twitching of skeletal muscles in the face and extremities. The likelihood of enflurane-induced seizure activity is increased when the concentration of enflurane is >2 MAC or when hyperventilation of the lungs decreases the PaCO_2 to <30 mm Hg. Repetitive auditory stimuli can also initiate seizure activity during the administration of enflurane. There is no evidence of anaerobic metabolism in the brain during seizure activity produced by enflurane. Furthermore, in an animal model, enflurane does not enhance preexisting seizure foci, with the possible exception being certain types of myoclonic epilepsy and photosensitive epilepsy.¹³²

Isoflurane does not evoke seizure activity on the EEG, even in the presence of deep levels of anesthesia, hypocapnia, or repetitive auditory stimulation. Indeed, isoflurane possesses anticonvulsant properties; it is able to suppress seizure activity produced by flurothyl.¹³³ An undocumented speculation is that the greater MAC value for enflurane compared with its isomer, isoflurane, reflects the need for a higher concentration to suppress the stimulating effects of enflurane in the CNS.

Desflurane and sevoflurane, like isoflurane, do not produce evidence of convulsive activity on the EEG either at deep levels of anesthesia or in the presence of hypocapnia or auditory stimulation. Nevertheless, there are reports of pediatric patients with epilepsy and otherwise healthy adults who developed EEG evidence of seizure activity during sevoflurane anesthesia.^{134,135} Sevoflurane can suppress convulsive activity induced with lidocaine.

The administration of nitrous oxide may increase motor activity with clonus and opisthotonus even in clinically used concentrations.¹³⁶ When nitrous oxide is administered in high concentrations in a hyperbaric chamber, abdominal muscle rigidity, catatonic movements of extremities, and periods of skeletal muscle activity may alternate with periods of skeletal muscle relaxation, clonus, and opisthotonus.¹³⁷ Although very rare, tonic-clonic seizure activity has been described after administration of nitrous oxide to an otherwise healthy child.¹³⁸ Animals suspended by their tails may experience seizures in the first 15 to 90 minutes after discontinuation of nitrous oxide but not of volatile anesthetics.¹³⁹ It is possible that these withdrawal seizures reflect acute nitrous oxide dependence. In patients, delirium or excitement during recovery from anesthesia that included nitrous oxide could reflect this phenomenon.

Evoked Potentials

Volatile anesthetics cause dose-related decreases in the amplitude and increases in the latency of the cortical component of median nerve somatosensory evoked potentials, visual evoked potentials, and auditory evoked potentials.^{140,141} Decreases in amplitude are more marked than increases in latencies. In the presence of 60% nitrous oxide, waveforms adequate for monitoring cortical somatosensory evoked potentials are present during administration of 0.50 to 0.75 MAC halothane and 0.5 to 1.0 MAC enflurane and isoflurane.¹⁴² Peri-MACs of desflurane (0.5-1.5 MAC) increasingly depress somatosensory evoked potentials in patients.⁴ Even nitrous oxide alone may decrease the amplitude of cortical somatosensory evoked potentials.

Mental Function and Awareness

By definition, inhaled anesthetics cause loss of response to verbal command at MAC-awake concentrations. Subtle effects on mental function (learning) may occur at lower anesthetic concentrations (0.2 MAC).¹⁴³ Gaseous anesthetics may not be equally effective in preventing awareness. For example, 0.4 MAC isoflurane prevents recall and responses to commands, whereas nitrous oxide requires greater than 0.5 to 0.6 MAC to produce similar effects. Surgical stimulation may increase the anesthetic requirement to prevent awareness.

Cerebral Blood Flow

Volatile anesthetics produce dose-dependent increases in CBF. The magnitude of this increase is dependent on the balance between the drug's intrinsic vasodilatory actions and vasoconstriction secondary to flow-metabolism coupling. Volatile anesthetics administered during normocapnia in concentrations of >0.6 MAC produce cerebral vasodilation, decreased cerebral vascular resistance, and resulting dose-dependent increases in CBF (Figure 4.24).¹²⁷ This drug-induced increase in CBF occurs despite concomitant decreases in cerebral metabolic requirements. Sevoflurane has an intrinsic dose-dependent cerebral vasodilatory effect, but this effect is less than that of isoflurane.¹⁴⁴ Desflurane and isoflurane are similar in terms of increases in CBF and the preservation of reactivity to carbon dioxide (Figure 4.25).¹⁴⁵ Nitrous oxide also increases CBF, but its restriction to concentrations of <1 MAC limits the magnitude of this change. In fact, nitrous oxide may be a more potent cerebral vasodilator than an equipotent dose of isoflurane alone in humans.¹⁴⁶

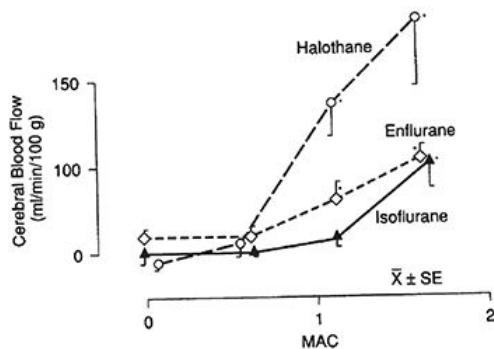


FIGURE 4.24 Cerebral blood flow measured in the presence of normocapnia and in the absence of surgical stimulation (* $P < .05$). Reprinted with permission from Eger EI. Isoflurane (Forane): A Compendium and

Reference. Madison, WI: Ohio Medical Products; 1985:1-110; Reprinted from Eger EI. The pharmacology of isoflurane. Br J Anaesth. 1984;56 (Suppl 1):71S-99S. Copyright © 1984 Elsevier. With permission.

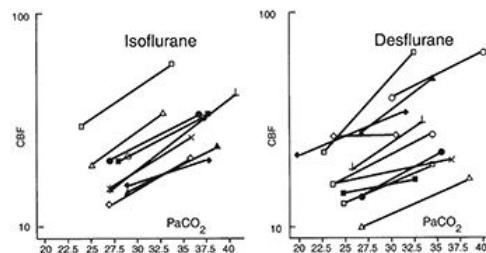


FIGURE 4.25 Individual cerebral blood flow (CBF) measurements (mL/100 g per minute) plotted against PaCO_2 (mm Hg) in patients receiving 1.25 minimal alveolar concentration isoflurane or desflurane. *Reprinted with permission from Ornstein E, Young WL, Fleischer LH, et al. Desflurane and isoflurane have similar effects on cerebral blood flow in patients with intracranial mass lesions. Anesthesiology. 1993;79(3):498-502. Copyright © 1993 American Society of Anesthesiologists, Inc.*

Anesthetic-induced increases in CBF occur within minutes of initiating administration of the inhaled drug and whether blood pressure is unchanged or decreased, emphasizing the cerebral vasodilating effects of these drugs. Animals exposed to halothane demonstrate a time-dependent return to baseline from the previously increased CBF beginning after about 30 minutes and reaching predrug levels after about 150 minutes.¹⁴⁷ This normalization of CBF reflects a concomitant increase in cerebral vascular resistance that is not altered by α - or β -adrenergic blockade and is not the result of changes in the pH of the cerebrospinal fluid.¹⁴⁸

Unlike the decay in CBF with time observed in animals, CBF remains increased relative to cerebral metabolic oxygen requirements for as long as 4 hours during administration of halothane, isoflurane, or sevoflurane to patients during surgery (see [Figure 4.25](#)).¹⁴⁹ Furthermore, in these patients, isoflurane possesses greater capability to maintain global CBF relative to cerebral metabolic oxygen requirements than does halothane or sevoflurane (see [Figure 4.24](#)).¹⁴⁹ An unchanging EEG during this period suggests that CBF is increased over time without decay rather than a parallel change in CBF and cerebral metabolic oxygen requirements.

Autoregulation of CBF in response to changes in systemic blood pressure is retained during administration of 1 MAC isoflurane but not halothane ([Figure 4.26](#)).¹²⁷ Inhaled anesthetics including desflurane and sevoflurane do not alter autoregulation of CBF as reflected by the responsiveness of the cerebral circulation to changes in PaCO_2 .^{144,150,151} For example, cerebrovascular carbon dioxide reactivity is described as intact during administration of 1 MAC desflurane.¹⁵² Nevertheless, others describe impairment of autoregulation by desflurane with 1.5 MAC nearly abolishing autoregulation.¹⁵³

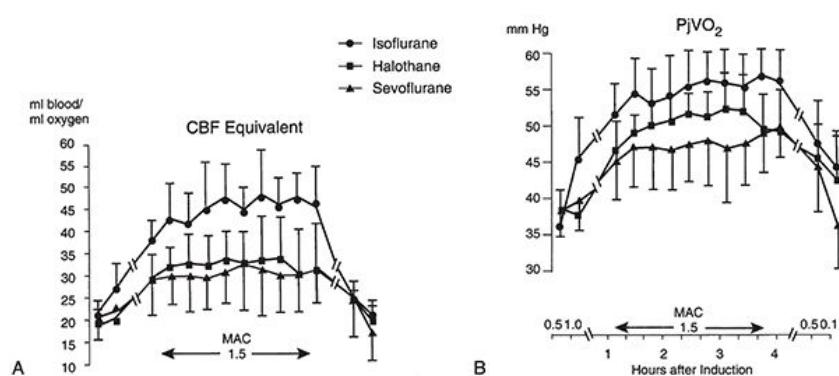


FIGURE 4.26 A, When compared at 1.5 minimal alveolar concentration (MAC), the average increase in cerebral blood flow (CBF) in the patients receiving isoflurane is greater than in those receiving halothane or sevoflurane. B, Likewise, the average value of the internal jugular venous oxygen tension ($PjVO_2$) is higher in patients receiving isoflurane. The increased CBF present at 1.5 MAC was sustained over time. *Reprinted with permission from Kuroda Y, Murakami M, Tsuruta J, et al. Preservation of the ratio of cerebral blood flow/metabolic rate for oxygen during prolonged anesthesia with isoflurane, sevoflurane, and halothane in humans. Anesthesiology. 1996;84(3):555-561. Copyright © 1996 American Society of Anesthesiologists, Inc.*

Cerebral Metabolic Oxygen Requirements

Inhaled anesthetics produce dose-dependent decreases in cerebral metabolic oxygen requirements that are greater during the administration of isoflurane than with an equivalent MAC of halothane.¹⁵⁴ When the EEG becomes isoelectric, an additional increase in the concentration of the volatile anesthetics does not produce further decreases in cerebral metabolic oxygen requirements. The greater decrease in cerebral metabolic oxygen requirements produced by isoflurane may explain why CBF is not predictably increased by this anesthetic at concentrations lower than 1 MAC. For example, decreased cerebral metabolism means less carbon dioxide is produced, which thus opposes any increase in CBF. It is conceivable that isoflurane could evoke unexpected increases in CBF if administered to a patient in whom cerebral metabolic oxygen requirements were already decreased by drugs. Desflurane and sevoflurane decrease cerebral metabolic oxygen requirements similar to isoflurane.

Cerebral Protection

Although neurologic outcome is not different based on the volatile anesthetic administered, these data suggest that relative to enflurane and halothane, isoflurane may offer a degree of cerebral protection (blunts necrotic processes resulting from cerebral ischemia) from transient incomplete regional cerebral ischemia during carotid endarterectomy.¹⁵⁵ Unchanged CBF and decreased cerebral metabolic oxygen requirements during isoflurane-induced controlled hypotension for clipping of cerebral aneurysms indicates that global cerebral oxygen supply-demand balance is favorably altered in patients anesthetized with this anesthetic.¹⁵⁶

Intracranial Pressure

Inhaled anesthetics produce increases in ICP that parallel increases in CBF produced by these drugs. Patients with space-occupying intracranial lesions are most vulnerable to these drug-induced increases in ICP. In hypocapnic humans with intracranial masses, desflurane concentrations of <0.8 MAC do not increase ICP, whereas 1.1 MAC increases ICP by 7 mm Hg.¹⁵⁷ Hyperventilation of the lungs to decrease the $Paco_2$ to about 30 mm Hg opposes the tendency for inhaled anesthetics to increase ICP.¹⁵⁸ With enflurane, it must be remembered that hyperventilation of the lungs increases the risk of seizure activity, which could lead to increased cerebral metabolic oxygen requirements and carbon dioxide production. These enflurane-induced changes will tend to increase CBF, which could further increase ICP. The ability of nitrous oxide to increase ICP is probably less than that of volatile anesthetics, reflecting the restriction of the dose of this drug to <1 MAC.

Cerebrospinal Fluid Production

Isoflurane does not alter production of CSF and, at the same time, decreases resistance to reabsorption.¹⁵⁹ These observations are consistent with minimal increases in ICP observed during the administration of isoflurane. Increases in ICP associated with administration of nitrous oxide presumably reflect increases in CBF because enhanced production of CSF does not occur in the presence of this inhaled anesthetic.¹⁶⁰

Circulatory Effects

Inhaled anesthetics produce dose-dependent and drug-specific circulatory effects. The circulatory effects of desflurane and sevoflurane parallel many of the characteristics of older inhaled anesthetics with desflurane

most closely resembling isoflurane, whereas sevoflurane has characteristics of both isoflurane and halothane.⁴¹⁶¹

Drug-induced circulatory effects manifest as changes in systemic blood pressure, heart rate, cardiac output, stroke volume, right atrial pressure, systemic vascular resistance, cardiac rhythm, and coronary blood flow. Circulatory effects of inhaled anesthetics may be different in the presence of (1) controlled ventilation of the lungs compared with spontaneous breathing, (2) preexisting cardiac disease, or (3) drugs that act directly or indirectly on the heart. The mechanisms of circulatory effects are diverse but often reflect the effects of inhaled anesthetics on (1) myocardial contractility, (2) peripheral vascular smooth muscle tone, and (3) autonomic nervous system activity (see the section “[Mechanisms of Circulatory Effects](#)”).

Mean Arterial Pressure

Halothane, isoflurane, desflurane, and sevoflurane produce similar and dose-dependent decreases in mean arterial pressure when administered to healthy human volunteers ([Figure 4.27](#)).¹⁶² The magnitude of decrease in mean arterial pressure in volunteers is greater than that which occurs in the presence of surgical stimulation. Likewise, artificially increased preoperative levels of systemic blood pressure, as may accompany apprehension, may be followed by decreases in blood pressure that exceed the true pharmacologic effect of the volatile anesthetic. In contrast with volatile anesthetics, nitrous oxide produces either no change or modest increases in systemic blood pressure.^{127,163} Substitution of nitrous oxide for a portion of the volatile anesthetic decreases the magnitude of blood pressure decrease produced by the same MAC of the volatile anesthetic alone ([Figure 4.28](#)).¹²⁷ The decrease in blood pressure produced by halothane is, in part or in whole, a consequence of decreases in myocardial contractility and cardiac output, whereas with isoflurane, desflurane, and sevoflurane, the decrease in systemic blood pressure results principally from a decrease in systemic vascular resistance (see the section “[Mechanism of Anesthesia-Induced Unconsciousness](#)”).

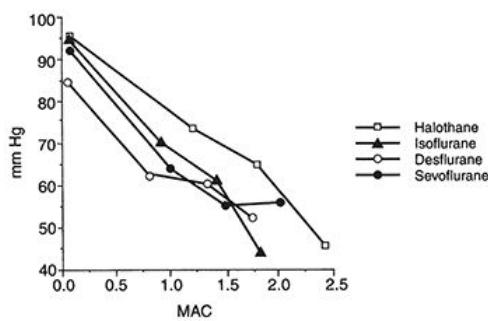


FIGURE 4.27 The effects of increasing concentrations (minimal alveolar concentration [MAC]) of halothane, isoflurane, desflurane, and sevoflurane on mean arterial pressure (mm Hg) when administered to healthy volunteers. Reprinted with permission from Cahalan MK. Hemodynamic Effects of Inhaled Anesthetics [Review Courses]. Cleveland, OH: International Anesthesia Research Society; 1996:14-18.

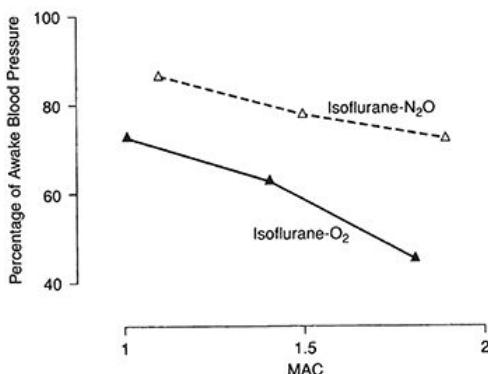


FIGURE 4.28 The substitution of nitrous oxide (N_2O) for a portion of isoflurane produces less decrease in blood pressure than the same dose of volatile anesthetic alone. Abbreviations: MAC, minimal alveolar concentration; O_2 , oxygen. *Reprinted with permission from Eger EI. Isoflurane (Forane): A Compendium and Reference. Madison, WI: Ohio Medical Products; 1985:1-110.*

Heart Rate

Isoflurane, desflurane, and sevoflurane, but not halothane, increase heart rate when administered to healthy human volunteers (Figure 4.29).¹⁶² Sevoflurane increases heart rate only at concentrations of >1.5 MAC, whereas isoflurane and desflurane tend to increase heart rate at lower concentrations. Heart rate effects seen in patients undergoing surgery may be quite different than those documented in volunteers because so many confounding variables influence heart rate. For example, a small dose of opioid (morphine in the preoperative medication or fentanyl intravenously immediately before induction of anesthesia) can prevent the heart rate increase associated with isoflurane and presumably the other volatile anesthetics (Figure 4.30).¹⁶⁴ Increased sympathetic nervous system activity, as accompanies apprehension, may artificially increase heart rate and the magnitude of the true pharmacologic effect of the volatile anesthetic. Similarly, excessive parasympathetic nervous system activity may result in unexpected increases in heart rate when anesthesia is established.

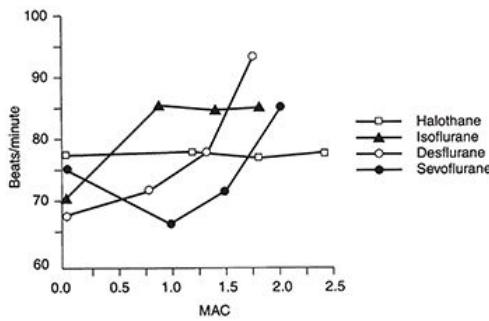


FIGURE 4.29 The effects of increasing concentrations (minimal alveolar concentration [MAC]) of halothane, isoflurane, desflurane, and sevoflurane on heart rate (beats per minute) when administered to healthy volunteers. *Reprinted with permission from Cahalan MK. Hemodynamic Effects of Inhaled Anesthetics [Review Courses]. Cleveland, OH: International Anesthesia Research Society; 1996:14-18.*

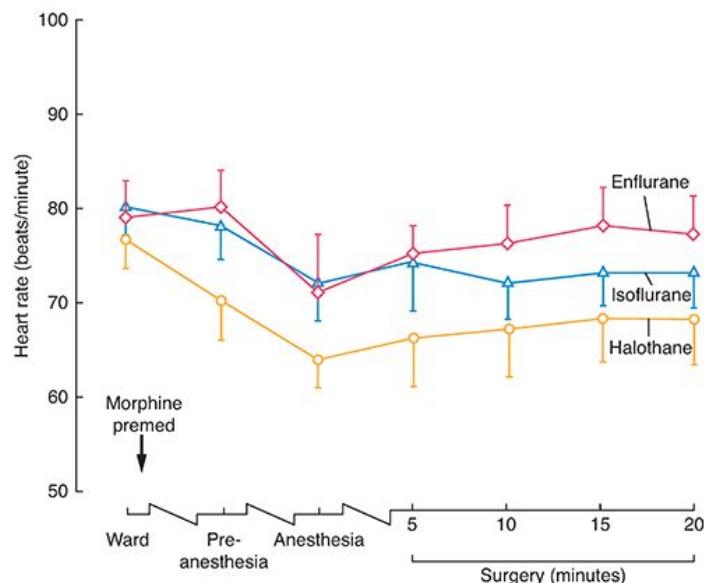


FIGURE 4.30 Morphine premedication is not associated with increases in heart rate (mean \pm standard error) during administration of volatile anesthetics with or without surgical stimulation. Reprinted with permission from Cahalan MK, Lurz FW, Eger EI II, et al. Narcotics decrease heart rate during inhalational anesthesia. Anesth Analg. 1987;66(2):166-170. Copyright © 1987 International Anesthesia Research Society.

The common observation of an unchanged heart rate despite a decrease in blood pressure during the administration of halothane may reflect depression of the carotid sinus (baroreceptor reflex response) by halothane as well as drug-induced decreases in the rate of sinus node depolarization. Junctional rhythm and associated decreases in systemic blood pressure most likely reflect suppression of sinus node activity by halothane. Halothane also decreases the speed of conduction of cardiac impulses through the atrioventricular node and His-Purkinje system. At 0.5 MAC, desflurane produces decreases in systemic blood pressure similar to those caused by isoflurane but does not evoke an increased heart rate as does isoflurane. This difference is not explained by disparate effects of these anesthetics on the baroreceptor-reflex response.¹⁶⁵ In neonates, administration of isoflurane is associated with attenuation of the carotid sinus reflex response, as reflected by drug-induced decreases in blood pressure that are not accompanied by increases in heart rate.¹⁶⁶ Heart rate responses during administration of isoflurane also seem to be blunted in elderly patients, whereas isoflurane-induced increases in heart rate are more likely to occur in younger patients and may be accentuated by the presence of other drugs (atropine, pancuronium) that exert vagolytic effects. Nitrous oxide also depresses the carotid sinus, but quantitating this effect is difficult because of its limited potency and its frequent simultaneous administration with other injected or inhaled drugs.

Cardiac Output and Stroke Volume

Halothane, but not isoflurane, desflurane, and sevoflurane, produces dose-dependent decreases in cardiac output when administered to healthy human volunteers (Figure 4.31).¹⁶⁷ Sevoflurane did decrease cardiac output at 1 and 1.5 MAC, but at 2 MAC, cardiac output had recovered to nearly awake values. Sevoflurane causes a smaller decrease in cardiac output than does halothane when administered to infants.¹⁶⁷ Due to different effects on heart rate (halothane causes no change and heart rate increases in the presence of the other volatile anesthetics), the calculated left ventricular stroke volume was similarly decreased 15% to 30% for all the volatile anesthetics. In patients, the increase in heart rate may tend to offset drug-induced decreases in cardiac output. Cardiac output is modestly increased by nitrous oxide, possibly reflecting the mild sympathomimetic effects of this drug.

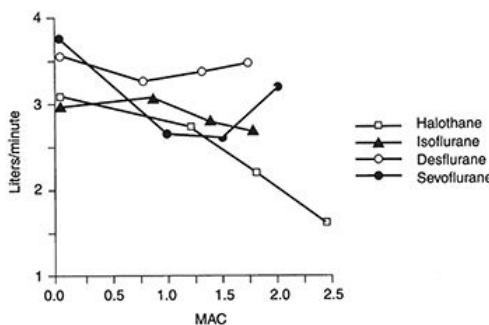


FIGURE 4.31 The effects of increasing concentrations (minimal alveolar concentration [MAC]) of halothane, isoflurane, desflurane, and sevoflurane on cardiac index (liters per minute) when administered to healthy volunteers. Reprinted with permission from Cahalan MK. Hemodynamic Effects of Inhaled Anesthetics [Review Courses]. Cleveland, OH: International Anesthesia Research Society; 1996:14-18.

In addition to better maintenance of heart rate, isoflurane's minimal depressant effects on cardiac output could reflect activation of homeostatic mechanisms that obscure direct cardiac depressant effects. Indeed, volatile anesthetics, including isoflurane, produce similar dose-dependent depression of myocardial contractility when studied in vitro using isolated papillary muscle preparations. The vasodilating effects of the ether-derivative volatile anesthetics make the direct myocardial depression produced by these drugs less

apparent than that of halothane. Indeed, excessive concentrations of these drugs administered to patients can produce cardiovascular collapse. In vitro depression of myocardial contractility produced by nitrous oxide is about one-half that produced by comparable concentrations of volatile anesthetics. Direct myocardial depressant effects *in vivo* are most likely offset by mild sympathomimetic effects of nitrous oxide.

Another possible explanation for the lesser impact of isoflurane on myocardial contractility may be its greater anesthetic potency relative to that of halothane.¹²⁷ For example, the multiple of MAC times the oil:gas partition coefficient for halothane is 168 and 105 for isoflurane. The implication is that isoflurane may more readily depress the brain and thus, at a given MAC value, appear to spare the heart. Indeed, in animals, the lesser myocardial depression associated with the administration of isoflurane manifests as a greater margin of safety between the dose that produces anesthesia and that which produces cardiovascular collapse.¹⁶⁸

Right Atrial Pressure

Halothane, isoflurane, and desflurane, but not sevoflurane, increase right atrial pressure (central venous pressure) when administered to healthy human volunteers but the changes are minimal at 1 MAC ([Figure 4.32](#)).¹⁶² These differences are not predictable based on the many other similarities between sevoflurane, desflurane, and isoflurane. The peripheral vasodilating effects of volatile anesthetics would tend to minimize the effects of direct myocardial depression on right atrial pressure produced by these drugs. Increased right atrial pressure during administration of nitrous oxide most likely reflects increased pulmonary vascular resistance due to the sympathomimetic effects of this drug.¹⁶⁹

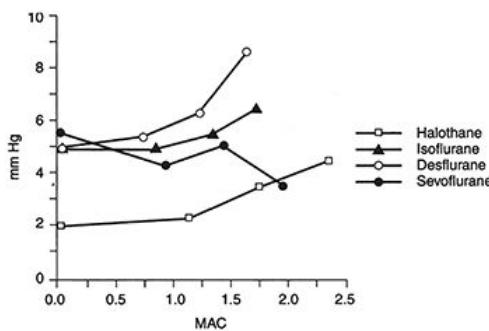


FIGURE 4.32 The effects of increasing concentrations (minimal alveolar concentration [MAC]) of halothane, isoflurane, desflurane, and sevoflurane on central venous pressure (mm Hg) when administered to healthy volunteers. Reprinted with permission from Cahalan MK. Hemodynamic Effects of Inhaled Anesthetics [Review Courses]. Cleveland, OH: International Anesthesia Research Society; 1996:14-18.

Systemic Vascular Resistance

Isoflurane, desflurane, and sevoflurane, but not halothane, decrease systemic vascular resistance when administered to healthy human volunteers ([Figure 4.33](#)).¹⁶² Thus, although these four volatile anesthetics decrease systemic blood pressure comparably, only halothane does so principally by decreasing cardiac output. For example, the absence of changes in systemic vascular resistance during administration of halothane emphasizes that decreases in systemic blood pressure produced by this drug parallelly decreases in myocardial contractility. The other volatile anesthetics decrease blood pressure principally by decreasing systemic vascular resistance. Nitrous oxide does not change systemic vascular resistance.

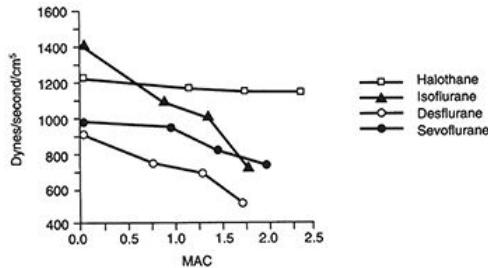


FIGURE 4.33 The effects of increasing concentrations (minimal alveolar concentration [MAC]) of halothane, isoflurane, desflurane, and sevoflurane on systemic vascular resistance (dynes/second/cm⁵) when administered to healthy volunteers. *Reprinted with permission from Cahalan MK. Hemodynamic Effects of Inhaled Anesthetics [Review Courses]. Cleveland, OH: International Anesthesia Research Society; 1996:14-18.*

Decreases in systemic vascular resistance during administration of isoflurane principally reflect substantial (up to fourfold) increases in skeletal muscle blood flow.¹⁷⁰ Cutaneous blood flow is also increased by isoflurane. The implications of these alterations in blood flow may include (1) excess (wasted) perfusion relative to oxygen needs, (2) loss of body heat due to increased cutaneous blood flow, and (3) enhanced delivery of drugs, such as muscle relaxants, to the neuromuscular junction.

Failure of systemic vascular resistance to decrease during administration of halothane does not mean that this drug lacks vasodilating effects on some organs. Clearly, halothane is a potent cerebral vasodilator and cutaneous vasodilation is prominent. These vasodilating effects of halothane, however, are offset by absent changes or vasoconstriction in other vascular beds such that the overall effect is unchanged calculated systemic vascular resistance.

The increase in cutaneous blood flow produced by all volatile anesthetics arterializes peripheral venous blood, providing an alternative to sampling arterial blood for evaluation of pH and Paco₂ (Figure 4.34).¹⁷¹ These drug-induced increases in cutaneous blood flow most likely reflect a central inhibitory action of these anesthetics on temperature-regulating mechanisms.

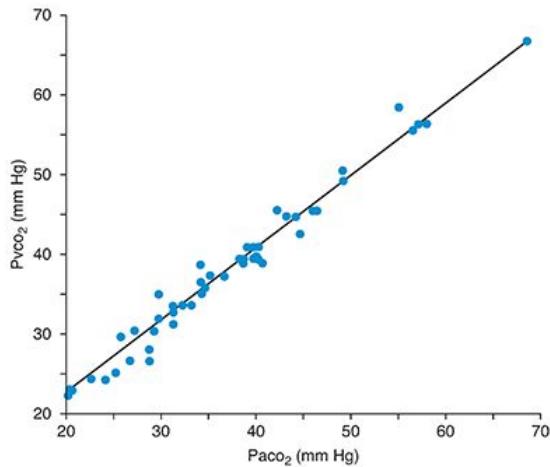


FIGURE 4.34 There is a linear relationship between PvCO₂ measured in “arterialized” peripheral venous blood and the Paco₂. *Reprinted with permission from Williamson DC III, Munson ES. Correlation of peripheral venous and arterial blood gas values during general anesthesia. Anesth Analg. 1982;61(11):950-952. Copyright © 1982 International Anesthesia Research Society.*

Pulmonary Vascular Resistance

Volatile anesthetics appear to exert little or no predictable effect on pulmonary vascular smooth muscle. Conversely, nitrous oxide may produce increases in pulmonary vascular resistance that is exaggerated in patients with preexisting pulmonary hypertension.^{172,173} The neonate with or without preexisting pulmonary hypertension may also be uniquely vulnerable to the pulmonary vascular vasoconstricting effects of nitrous oxide.¹⁷⁴ In patients with congenital heart disease, these increases in pulmonary vascular resistance may increase the magnitude of right-to-left intracardiac shunting of blood and further jeopardize arterial oxygenation.

Cardiac Dysrhythmias

The ability of volatile anesthetics to decrease the dose of epinephrine necessary to evoke ventricular cardiac dysrhythmias is greatest with the alkane derivative halothane and minimal to nonexistent with the ether derivatives isoflurane, desflurane, and sevoflurane (**Figure 4.35**).^{175–177}

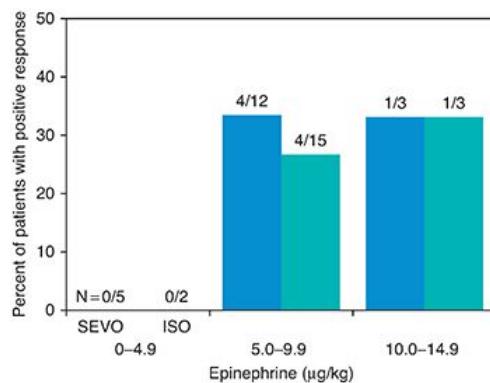


FIGURE 4.35 Responses to submucosally injected epinephrine in patients receiving sevoflurane (SEVO) or isoflurane (ISO) anesthesia. Reprinted with permission from Navarro R, Weiskopf RB, Moore MA, et al. Humans anesthetized with sevoflurane or isoflurane have similar arrhythmic response to epinephrine. Anesthesiology. 1994;80(3):545-549. Copyright © 1994 American Society of Anesthesiologists, Inc.

QTc Interval

Halothane, enflurane, and isoflurane prolong the QTc interval on the electrocardiogram in healthy patients.¹⁷⁸ Nevertheless, similar changes may not occur in patients with idiopathic long QTc interval syndrome suggesting that generalizations from healthy patients to patients with long QTc interval syndrome may not be valid. Conversely, there are reports of patients with long QTc syndrome of prolongation of the QT interval in response to the administration of sevoflurane.^{179,180} Furthermore, in healthy patients, administration of sevoflurane, but not propofol, results in prolongation of the QTc interval on the electrocardiogram.¹⁸¹

Accessory Pathway Conduction

The technology that underlies electrophysiologic studies and treatments is beyond the purview of this text but is covered in a recent review.¹⁸² The choice of anesthetic and monitoring depends on the pathophysiology underlying the arrhythmia being treated. Sympathetically driven arrhythmias such as supraventricular tachycardia and ventricular tachycardia are challenging because they are suppressed by most anesthetic agents as they reduce adrenergic tone. Volatile anesthetics are the most commonly used and cause minimal interference. Propofol can suppress atrial fibrillation in children and can be used to suppress electrical storm. There is no evidence that ketamine inhibits arrhythmias. It does not alter sinoatrial or atrioventricular node function but stimulates hemodynamics through adrenergic stimulation.

Spontaneous Breathing

Circulatory effects produced by volatile anesthetics during spontaneous breathing are different from those observed during normocapnia and controlled ventilation of the lungs. This difference reflects the impact of

sympathetic nervous system stimulation due to accumulation of carbon dioxide (respiratory acidosis) and improved venous return during spontaneous breathing. In addition, carbon dioxide may have direct relaxing effects on peripheral vascular smooth muscle. Indeed, systemic blood pressure, and heart rate are increased and systemic vascular resistance is decreased compared with measurements during administration of volatile anesthetics in the presence of controlled ventilation of the lungs to maintain normocapnia.^{183–185}

Coronary Blood Flow

Volatile anesthetics induce coronary vasodilation by preferentially acting on vessels with diameters from 20 to 50 microns, whereas adenosine, in addition, has a pronounced impact on the small precapillary arterioles.¹⁸⁶ It has been suggested that isoflurane as well as other coronary vasodilators (adenosine, dipyridamole, nitroprusside) that preferentially dilate the small coronary resistance coronary vessels would be capable of redistributing blood from ischemic to nonischemic areas, producing the phenomenon known as **coronary steal syndrome**. Nevertheless, this phenomenon is not clinically significant and volatile anesthetics, including isoflurane, are cardioprotective (see the section “[Cardiac Protection \[Anesthetic Preconditioning\]](#)”).

Neurocirculatory Responses

The solubility characteristics of desflurane make this volatile anesthetic a good choice to treat abrupt increases in systemic blood pressure and/or heart rate as may occur in response to sudden changes in the intensity of surgical stimulation. Nevertheless, abrupt increases in the alveolar concentrations of isoflurane and desflurane from 0.55 (0.71% isoflurane and 4% desflurane) to 1.66 MAC (2.12% isoflurane and 12% desflurane) increase sympathetic nervous system and renin-angiotensin activity and cause transient increases in mean arterial pressure and heart rate ([Figures 4.36](#) to [4.38](#)).¹⁸⁷ Desflurane causes significantly greater increases than isoflurane. The magnitude of the response to a rapid increase from 4% to 8% desflurane was similar to that produced by a rapid increase from 4% to 12%, suggesting that the stimulus provided by 8% desflurane produced a maximum response. Small (1%) increases in the desflurane concentration also transiently increase systemic blood pressure and heart rate, but the magnitude is less than those same changes that occur with an increase from 4% to 12%.¹⁸⁸ Sites mediating sympathetic nervous system activation in response to desflurane are present in the upper airway (larynx and above) and in the lungs.¹⁸⁹ These sites may respond to direct irritation. The increase in basal levels of sympathetic nervous system activity that accompany increasing inhaled concentrations of desflurane does not reflect the effects of drug-induced hypotension or alterations in baroreceptor activity.

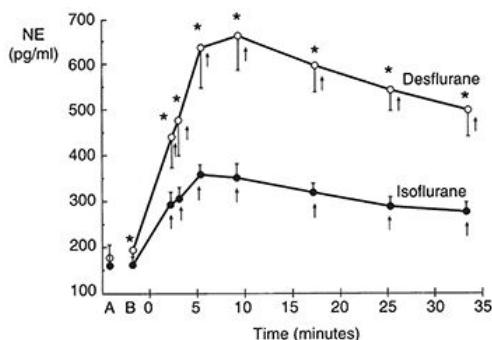


FIGURE 4.36 Plasma norepinephrine (NE) concentrations increased from awake levels (A) and those present during administration of 0.55 minimal alveolar concentration (MAC) desflurane or isoflurane (B) when the anesthetic concentrations were abruptly increased to 1.66 MAC (0). The increase was greater in the presence of desflurane than isoflurane (* $P < .05$). (Data are mean \pm standard error.) Reprinted with permission from Weiskopf RB, Moore MA, Eger EI II, et al. Rapid increase in desflurane concentration is associated with greater transient cardiovascular stimulation than with rapid increase in isoflurane concentration in humans. Anesthesiology. 1994;80(5):1035-1045. Copyright © 1994 American Society of Anesthesiologists, Inc.

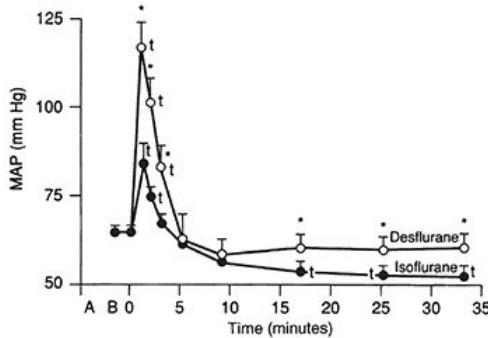


FIGURE 4.37 An abrupt and sustained increase in the concentration of desflurane from 0.55 to 1.66 minimal alveolar concentration (MAC) (0) resulted in a substantial but transient increase in mean arterial pressure (MAP). A similar increase in isoflurane MAC produced an increase in MAP that was substantially less than that observed in patients receiving desflurane. Within 5 minutes after increasing the anesthetic concentration, the MAP had decreased below awake (A) and 0.55 MAC values (B) reflecting the greater depth of anesthesia present at this time (t , $P < .05$ compared with the value at 0.55 MAC of the same anesthetic; * $P < .05$ compared with isoflurane at the same time point). *Reprinted with permission from Weiskopf RB, Moore MA, Eger EI II, et al. Rapid increase in desflurane concentration is associated with greater transient cardiovascular stimulation than with rapid increase in isoflurane concentration in humans. Anesthesiology. 1994;80(5):1035-1045. Copyright © 1994 American Society of Anesthesiologists, Inc.*

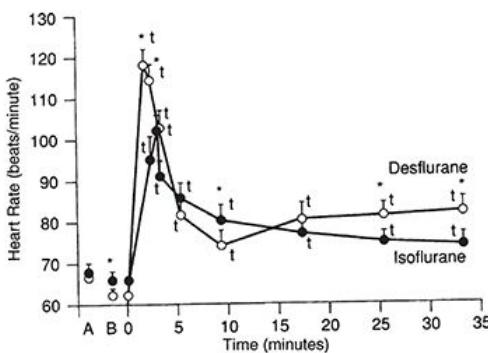


FIGURE 4.38 An abrupt and sustained increase in the concentration of desflurane from 0.55 to 1.66 minimal alveolar concentration (MAC) (0) resulted in a substantial but transient increase in heart rate. A similar increase in isoflurane MAC produced an increase in heart rate that was substantially less than that observed in patients receiving desflurane. Within 5 minutes after increasing the anesthetic concentration, the heart rate remained above awake (A) and baseline values at 0.55 MAC (B), reflecting the greater depth of anesthesia present at this time (t , $P < .05$ compared with the value at 0.55 MAC of the same anesthetic; * $P < .05$ compared with isoflurane at the same time point). *Reprinted with permission from Weiskopf RB, Moore MA, Eger EI II, et al. Rapid increase in desflurane concentration is associated with greater transient cardiovascular stimulation than with rapid increase in isoflurane concentration in humans. Anesthesiology. 1994;80(5):1035-1045. Copyright © 1994 American Society of Anesthesiologists, Inc.*

In contrast to desflurane and isoflurane, neurocirculatory responses do not accompany abrupt increases in the delivered concentration of sevoflurane ([Figure 4.39](#)).¹⁹⁰

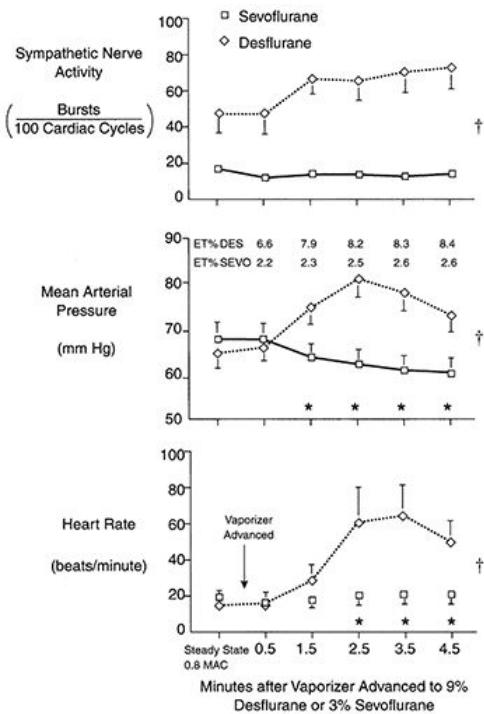


FIGURE 4.39 A rapid increase in the inspired concentration of sevoflurane (SEVO) from 0.8 minimal alveolar concentration (MAC) to 3% did not alter sympathetic nerve activity, mean arterial pressure, or heart rate. Conversely, a rapid increase in the inspired concentration of desflurane (DES) from 0.8 MAC to 9% significantly increased sympathetic nerve activity, mean arterial pressure, and heart rate. (Data are mean \pm standard error; * $P < .05$.) Abbreviation: ET, end-tidal. Reprinted with permission from Ebert TJ, Muzi M, Lopatka CW. Neurocirculatory responses to sevoflurane in humans: a comparison to desflurane. Anesthesiology. 1995;83(1):88-95. Copyright © 1995 American Society of Anesthesiologists, Inc.

Fentanyl (1.5–4.5 $\mu\text{g}/\text{kg}$ IV administered 5 minutes before the abrupt increase in desflurane concentration), esmolol (0.75 $\mu\text{g}/\text{kg}$ IV 1.5 minutes before), and clonidine (4.3 $\mu\text{g}/\text{kg}$ orally 90 minutes before) blunt the transient cardiovascular responses to rapid increases in desflurane concentration.¹⁹¹ Fentanyl may be the most clinically useful of these drugs because it blunts the increase in heart rate and blood pressure, has minimal cardiovascular depressant effects, and imposes little postanesthetic sedation. Alfentanil, 10 $\mu\text{g}/\text{kg}$ IV, in conjunction with the induction of anesthesia, also blunts the hemodynamic responses to an abrupt increase in the delivered concentration of desflurane; however, the increase in plasma norepinephrine concentrations that accompany the abrupt increase in desflurane concentration are not predictably prevented by the prior administration of opioids.¹⁹²

Preexisting Diseases and Drug Therapy

Preexisting cardiac disease may influence the significance of circulatory effects produced by inhaled anesthetics. For example, volatile anesthetics decrease myocardial contractility of normal and failing cardiac muscle by similar amounts, but the significance is greater in diseased cardiac muscle because contractility is decreased even before administration of depressant anesthetics. Neurocirculatory responses evoked by abrupt increases in the concentration of desflurane may be undesirable in patients with coronary artery disease. In patients with coronary artery disease, administration of 40% nitrous oxide produces evidence of myocardial depression that does not occur in patients without heart disease.¹⁹³ Valvular heart disease may influence the significance of anesthetic-induced circulatory effects. For example, peripheral vasodilation produced by isoflurane (presumably also desflurane and sevoflurane) is undesirable in patients with aortic stenosis but may be beneficial by providing afterload reduction in those with mitral or aortic regurgitation. Arterial hypoxemia may enhance the cardiac depressant effects of volatile anesthetics.

Prior drug therapy that alters sympathetic nervous system activity (antihypertensives, β -adrenergic antagonists) may influence the magnitude of circulatory effects produced by volatile anesthetics. Calcium entry blockers decrease myocardial contractility and thus render the heart more vulnerable to direct depressant effects of inhaled anesthetics.

Mechanisms of Circulatory Effects

There is no known single mechanism that explains the cardiovascular depressant effects of volatile anesthetics, just as there is none for the neurobehavioral effects. Proposed mechanisms include (1) direct myocardial depression, (2) inhibition of CNS sympathetic activity, (3) peripheral autonomic ganglion blockade, (4) attenuated carotid sinus reflex activity, (5) decreased formation of cyclic adenosine monophosphate, (6) decreased release of catecholamines, and (7) decreased influx of calcium ions through slow channels. Indeed, negative inotropic, vasodilating, and depressant effects on the sinoatrial node produced by volatile anesthetics are similar to the effects produced by calcium entry blockers.¹⁹⁴ However, voltage-gated calcium channels are only inhibited to a small extent by inhalational anesthetics.¹⁹⁵ Plasma catecholamine concentrations typically do not increase during administration of volatile anesthetics except during the initiation of desflurane anesthesia and isoflurane anesthesia to some extent, which is evidence that these drugs do not activate and may even decrease activity of the central and peripheral sympathetic nervous systems.

Isoflurane may be unique among the volatile anesthetics in possessing mild β -adrenergic agonist properties. This effect is consistent with the maintenance of cardiac output, increased heart rate, and decreased systemic vascular resistance that may accompany administration of isoflurane.¹⁷⁰ The increase in blood pressure that is associated with rapid increases in desflurane concentration is accompanied by a significant increase in plasma epinephrine suggesting enhanced release from the adrenal gland.¹⁹¹

Nitrous oxide administered alone or added to unchanging concentrations of volatile anesthetics produces signs of mild sympathomimetic stimulation characterized by (1) increases in the plasma concentrations of catecholamines, (2) mydriasis, (3) increases in body temperature, (4) diaphoresis, (5) increases in right atrial pressure, and (6) evidence of vasoconstriction in the systemic and pulmonary circulations. Sympathetic nervous system stimulation may also result because nitrous oxide can inhibit uptake of norepinephrine by the lungs, making more neurotransmitter available to receptors.¹⁹⁶ Interestingly, nitrous oxide shares its sympathomimetic aspect with another NMDA-blocking anesthetic, ketamine.

In contrast to sympathomimetic effects observed with the administration of nitrous oxide alone or added to volatile anesthetics, the inhalation of nitrous oxide in the presence of opioids results in evidence of profound circulatory depression, characterized by decreases in systemic blood pressure and cardiac output and increases in left ventricular end-diastolic pressure and systemic vascular resistance.^{197,198} It is possible that opioids inhibit the centrally mediated sympathomimetic effects of nitrous oxide, thus unmasking its direct depressant effects on the heart.

Cardiac Protection (Anesthetic Preconditioning)

Brief episodes of myocardial ischemia occurring before a subsequent longer period of myocardial ischemia providing protection against myocardial dysfunction and necrosis is termed *ischemic preconditioning*.¹⁹⁹ The molecular mechanism that underlies this phenomenon has been defined for more than 20 years because each step in the pathway represents a target for cardiac protection. Over the years, thousands of molecules have been defined that induce interaction between myocardial organelles and other cells including neurons, lymphocytes (**Figure 4.40**).²⁰⁰ It has been difficult to define a succinct description because of the voluminous number of players that interact over an almost instantaneous time course. See Heursh²⁰⁰ for review. However, these findings brought forth the concept of ischemic preconditioning that has been demonstrated in other organs including the kidneys.

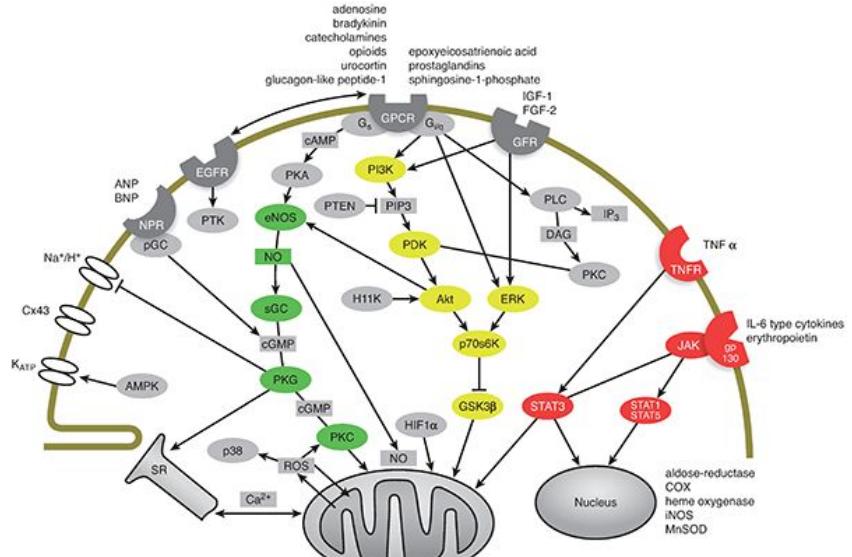


FIGURE 4.40 Proteins implicated in cardiac protection. Reprinted with permission from Heusch G. Molecular basis of cardioprotection: signal transduction in ischemic pre-, post-, and remote conditioning. Circ Res. 2015;116(4):674-699. Copyright © 2015 American Heart Association, Inc.

Ventilation Effects

Inhaled anesthetics produce dose-dependent and drug-specific effects on the (1) pattern of breathing, (2) ventilatory response to carbon dioxide, (3) ventilatory response to arterial hypoxemia, and (4) airway resistance. The PaO_2 predictably declines during administration of inhaled anesthetics in the absence of supplemental oxygen.

Pattern of Breathing

Inhaled anesthetics, except for isoflurane, produce dose-dependent increases in the frequency of breathing.²⁰¹ Isoflurane increases the frequency of breathing similarly to other inhaled anesthetics up to a dose of 1 MAC. At a concentration of >1 MAC, however, isoflurane does not produce a further increase in the frequency of breathing. Nitrous oxide increases the frequency of breathing more than other inhaled anesthetics at concentrations of >1 MAC. The effect of inhaled anesthetics on the frequency of breathing presumably reflects CNS stimulation. Volatile anesthetics stimulate central respiratory chemoreceptor neurons likely through activation of THIK-1 (potassium channel subfamily K member 13; K2p13.1) receptors, a two-pore potassium channel that is responsible for a background potassium current.²⁰² Activation of pulmonary stretch receptors by inhaled anesthetics has not been demonstrated. The exception may be nitrous oxide, which, at anesthetic concentrations of >1 MAC, may also stimulate pulmonary stretch receptors.

Tidal volume is decreased in association with anesthetic-induced increases in the frequency of breathing. The net effect of these changes is a rapid and shallow pattern of breathing during general anesthesia. The increase in frequency of breathing is insufficient to offset decreases in tidal volume, leading to decreases in minute ventilation and increases in Paco_2 . The pattern of breathing during general anesthesia is also characterized as regular and rhythmic in contrast to the awake pattern of intermittent deep breaths separated by varying intervals.

Ventilatory Response to Carbon Dioxide

Volatile anesthetics produce dose-dependent depression of ventilation characterized by decreases in the ventilatory response to carbon dioxide and increases in the Paco_2 (Figure 4.41).¹ Desflurane and sevoflurane depress ventilation, producing profound decreases in ventilation leading to apnea between 1.5 and 2.0 MAC.

Both of these volatile anesthetics increase Paco_2 and decrease the ventilatory response to carbon dioxide. Depression of ventilation produced by anesthetic concentrations up to 1.24 MAC desflurane are similar to the depression produced by isoflurane.²⁰³

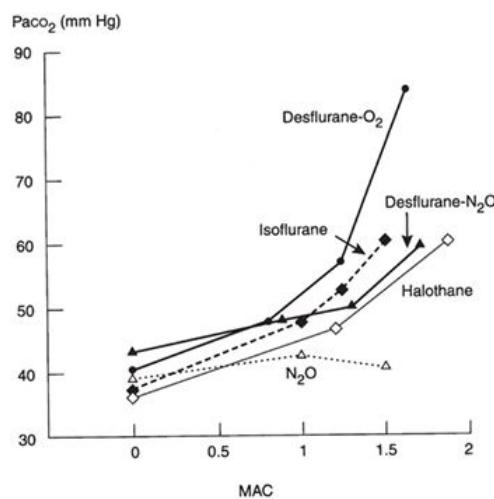


FIGURE 4.41 Inhaled anesthetics produce drug-specific and dose-dependent increases in Paco_2 . Abbreviations: MAC, minimal alveolar concentration; O₂, oxygen; N₂O, nitrous oxide. *Derived from Eger EI. Desflurane (Suprane): A Compendium and Reference. Nutley, NJ: Anaquest; 1993:1-119.*

The presence of chronic obstructive pulmonary disease (COPD) may accentuate the magnitude of increase in Paco_2 produced by volatile anesthetics.²⁰⁴ Nitrous oxide does not increase the Paco_2 , suggesting that substitution of this anesthetic for a portion of the volatile anesthetic would result in less depression of ventilation. Indeed, nitrous oxide combined with a volatile anesthetic produces less depression of ventilation and increase in Paco_2 than does the same MAC of the volatile drug alone.²⁰⁵ This ventilatory depressant-sparing effect of nitrous oxide is detectable with all volatile anesthetics.¹

Despite the apparent benign effect of nitrous oxide on ventilation, the slope of the carbon dioxide response curve is decreased similarly and shifted to the right by anesthetic concentrations of all inhaled anesthetics (**Figure 4.42**).¹ Subanesthetic concentrations (0.1 MAC) of inhaled anesthetics, however, do not alter the ventilatory response to carbon dioxide. In addition to nitrous oxide, painful stimulation (surgical skin incision) and duration of drug administration influence the magnitude of increase in Paco_2 produced by volatile anesthetics.

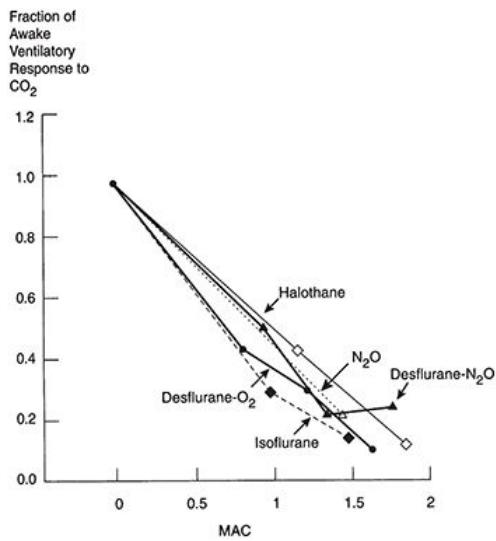


FIGURE 4.42 All inhaled anesthetics produce similar dose-dependent decreases in the ventilatory response to carbon dioxide (CO_2). Abbreviations: MAC, minimal alveolar concentration; O_2 , oxygen; N_2O , nitrous oxide. *Derived from Eger EI. Desflurane (Suprane): A Compendium and Reference. Nutley, NJ: Anaquest; 1993:1-119.*

Surgical Stimulation

Surgical stimulation increases minute ventilation by about 40% because of increases in tidal volume and frequency of breathing. The PaCO_2 , however, decreases only about 10% (4-6 mm Hg) despite the larger increase in minute ventilation (Figure 4.43).¹²⁷ The reason for this discrepancy is speculated to be an increased production of carbon dioxide resulting from activation of the sympathetic nervous system in response to painful surgical stimulation. Increased production of carbon dioxide is presumed to offset the impact of increased minute ventilation on PaCO_2 .

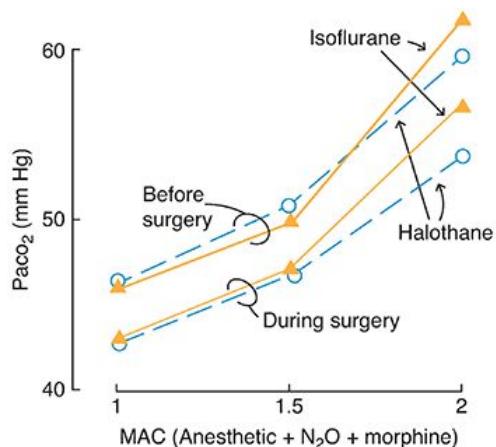


FIGURE 4.43 Impact of surgical stimulation on the resting PaCO_2 (mm Hg) during administration of isoflurane or halothane. Abbreviations: MAC, minimal alveolar concentration; N_2O , nitrous oxide. *Reprinted with permission from Eger EI. Isoflurane (Forane): A Compendium and Reference. 2nd ed. Madison, WI: Ohio Medical Products; 1981:1-110.*

Duration of Administration

After about 5 hours of administration, the increase in Paco_2 produced by spontaneous breathing of a volatile anesthetic is less than that present during administration of the same concentration for 1 hour (**Table 4.8**).¹⁸⁴ Likewise, the slope and position of the carbon dioxide response curve returns toward normal after about 5 hours of administration of the volatile anesthetics.²⁰⁵ The reason for this apparent recovery from the ventilatory depressant effects of volatile anesthetics with time is not known.

TABLE 4.8

Metabolism of volatile anesthetics as assessed by metabolite recovery versus mass balance studies^a

Anesthetic	Magnitude of metabolism	
	Metabolite recovery (%)	Mass balance (%)
Nitrous oxide	0.004	
Halothane	15-20	46.1
Enflurane	3	8.5
Isoflurane	0.2	0 ^b
Desflurane	0.02	
Sevoflurane	5	

^aData adapted from Carpenter RL, Eger EI II, Johnson BH, Unadkat JD, Sheiner LB. The extent of metabolism of inhaled anesthetics in humans. *Anesthesiology*. 1986;65:201-205.

^bMetabolism of isoflurane assumed to be 0 for this calculation.

Mechanism of Depression

Anesthetic-induced depression of ventilation as reflected by increases in the Paco_2 most likely reflects the direct depressant effects of these drugs on the medullary ventilatory center. An additional mechanism may be the ability of halothane and possibly other inhaled anesthetics to selectively interfere with intercostal muscle function, contributing to loss of chest wall stabilization during spontaneous breathing.²⁰⁶ This loss of chest wall stabilization could interfere with expansion of the chest in response to chemical stimulation of ventilation as normally produced by increases in the Paco_2 or arterial hypoxemia. Furthermore, this loss of chest wall stabilization means the descent of the diaphragm tends to cause the chest to collapse inward during inspiration, contributing to decreases in lung volumes, particularly the FRC. It is thus likely that halothane-induced depression of ventilation reflects both central and peripheral effects of the drug. The ventilatory depression associated with sevoflurane may result from a combination of central depression of medullary inspiratory neurons and depression of diaphragmatic function and contractility.²⁰⁷

Management of Ventilatory Depression

The predictable ventilatory depressant effects of volatile anesthetics are most often managed by institution of mechanical (controlled) ventilation of the patient's lungs. In this regard, the inherent ventilatory depressant effects of volatile anesthetics facilitate the initiation of controlled ventilation.²⁰⁸

Ventilatory Response to Hypoxemia

All inhaled anesthetics, including nitrous oxide, profoundly depress the ventilatory response to hypoxemia that is normally mediated by the carotid bodies. For example, 0.1 MAC produces 50% to 70% depression, and 1.1 MAC produces 100% depression of this response.^{209,210} This contrasts with the absence of significant depression of the ventilatory response to carbon dioxide during administration of 0.1 MAC of volatile anesthetics. Inhaled anesthetics also attenuate the usual synergistic effect of arterial hypoxemia and hypercapnia on stimulation of ventilation. Sevoflurane-induced decreases in hypoxic responses are not different in men and women that contrasts with morphine, which produces greater depression of the ventilatory response to hypoxia in women.²¹¹ Sevoflurane is useful during thoracic surgery as it is a potent

bronchodilator, its low blood-gas solubility permits rapid adjustment of the depth of anesthesia, and effects on hypoxic pulmonary vasoconstriction are small.²¹²

Airway Resistance and Irritability

Risk factors for developing bronchospasm during anesthesia include young age (<10 years), perioperative respiratory infection, endotracheal intubation, and the presence of COPD.²¹³ Nevertheless, isoflurane and sevoflurane produce bronchodilation in patients with COPD (**Figure 4.44**).²¹⁴ Sevoflurane causes moderate bronchodilation that is not observed in patients receiving desflurane or thiopental (**Figure 4.45**).²¹⁵ Bronchoconstriction produced by desflurane is most likely to occur in patients who smoke (**Figure 4.46**).²¹⁵ Administration of fentanyl 1 µg/kg IV or morphine 100 µg/kg IV prior to inhalation induction with desflurane and nitrous oxide significantly decreases airway irritability associated with desflurane.²¹⁶ After tracheal intubation in patients without asthma, airway resistance decreased in the presence of 1.1 MAC isoflurane, halothane, or sevoflurane (**Figure 4.47**).²¹⁷ Sevoflurane and desflurane have been administered without evidence of bronchospasm to patients with bronchial asthma.⁴

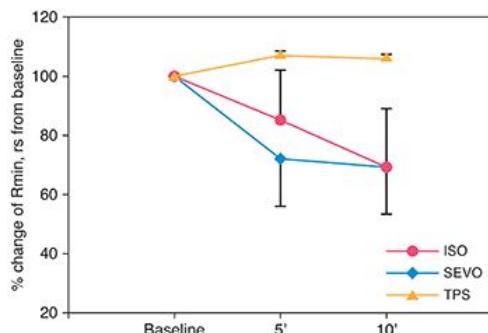


FIGURE 4.44 The percentage change (mean \pm standard deviation) in respiratory system resistance (R_{min} , rs) after 5 and 10 minutes of maintenance of anesthesia with thiopental (TPS), 1.1 minimal alveolar concentration (MAC) isoflurane (ISO) or 1.1 MAC sevoflurane (SEVO) administered to patients with chronic obstructive pulmonary disease. *Reprinted with permission from Volta CA, Alvisi V, Petrini S, et al. The effect of volatile anesthetics on respiratory system resistance in patients with chronic obstructive pulmonary disease. Anesth Analg. 2005;100(2):348-353.* Copyright © 2005 International Anesthesia Research Society.

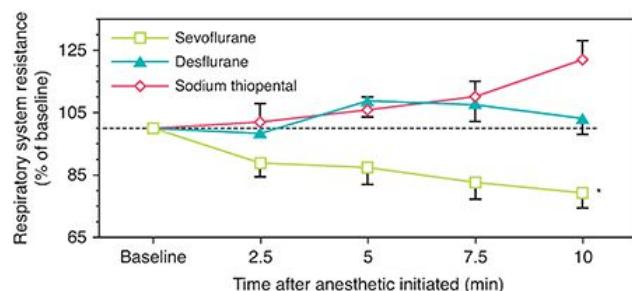


FIGURE 4.45 Changes in respiratory system resistance as a percentage of the thiopental baseline recorded after tracheal intubation but before the addition of sevoflurane or desflurane to the inhaled gases or beginning the infusion of thiopental. Airway resistance responses to sevoflurane were significantly different from desflurane and thiopental (* $P < .05$). *Reprinted with permission from Goff MJ, Arain SR, Ficke DJ, et al. Absence of bronchodilation during desflurane anesthesia: a comparison to sevoflurane and thiopental. Anesthesiology. 2000;93(2):404-408.* Copyright © 2000 American Society of Anesthesiologists, Inc.

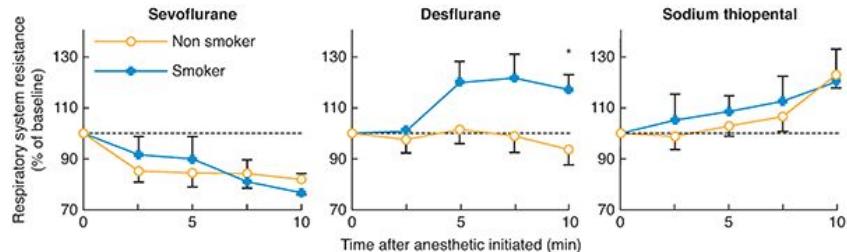


FIGURE 4.46 Respiratory system resistance during the 10 minutes after thiopental (baseline) based on current smoking status. Administration of desflurane to patients who were smokers was associated with significant bronchoconstriction compared with nonsmokers receiving desflurane (* $P < .05$). Reprinted with permission from Goff MJ, Arain SR, Ficke DJ, et al. Absence of bronchodilation during desflurane anesthesia: a comparison to sevoflurane and thiopental. *Anesthesiology*. 2000;93(2):404-408. Copyright © 2000 American Society of Anesthesiologists, Inc.

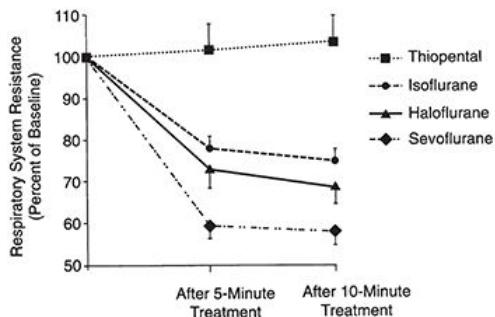


FIGURE 4.47 Respiratory system resistance decreased in the presence of 1.1 minimal alveolar concentration isoflurane, halothane, or sevoflurane, whereas no change occurred in patients receiving thiopental 0.25 mg/kg per minute plus 50% nitrous oxide. Reprinted with permission from Rooke GA, Choi JH, Bishop MJ. The effect of isoflurane, halothane, sevoflurane, and thiopental/nitrous oxide on respiratory system resistance after tracheal intubation. *Anesthesiology*. 1997;86(6):1294-1299. Copyright © 1997 American Society of Anesthesiologists, Inc.

The assessment of the cough response to tracheal stimulation by endotracheal tube cuff inflation is a reliable and clinically meaningful measure of upper airway reactivity. At 1 MAC, sevoflurane is superior to desflurane for suppressing moderate and severe responses to this stimulus (Figure 4.48).²¹⁸ However, the irritant effects of desflurane are thought to be as a result of stimulation of TRPA1 receptors in the airways.²¹⁹ Administration of desflurane, 1.8% to 5.4%, does not produce secretions, coughing, or breath holding in human volunteers.¹

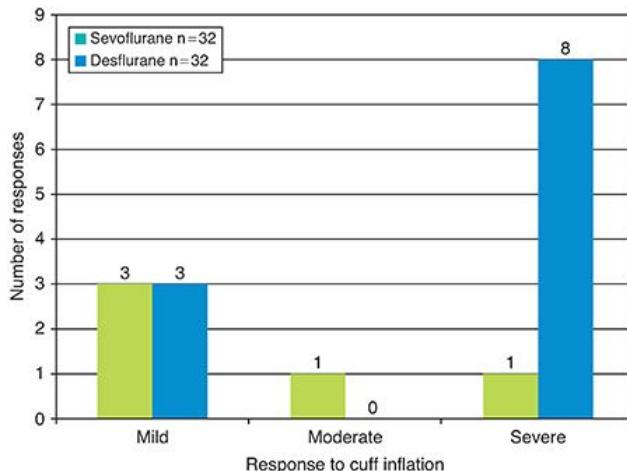


FIGURE 4.48 Responses to tracheal tube cuff inflation during 1 minimal alveolar concentration anesthesia with sevoflurane or desflurane. Reprinted with permission from Klock PA Jr, Czeslick EG, Klafta JM, et al. The effect of sevoflurane and desflurane on upper airway reactivity. Anesthesiology. 2001;94(6):963-967. Copyright © 2001 American Society of Anesthesiologists, Inc.

Despite the typical lack of irritant effects of sevoflurane on the airways, there is evidence that exposure of sevoflurane to desiccated carbon dioxide absorbents, especially those containing potassium hydroxide, may result in production of toxic gases and subsequent inhalation of these products causing airway irritation and impaired gas exchange.^{18,220} This airway irritation may be caused by formaldehyde, which is generated in isomolar concentrations with methanol. Compound A is not an airway irritant.

In the absence of bronchoconstriction, the bronchodilating effects of volatile anesthetics are difficult to demonstrate because normal bronchomotor tone is low and only minimal additional relaxation is possible. Like other inhaled anesthetics, nitrous oxide decreases FRC.

Neurologic Effects

Since the 1960s—largely sparked by the work of Wells and Keats²²¹ and their association of general anesthesia with a resultant increase in tolerance to cerebral ischemia during carotid occlusion—inhaled anesthetics have been considered to be neuroprotective agents. Multiple studies have been performed, and the results yielded positive association between neuroprotective characteristics of inhaled anesthetics.^{155,222} These findings were not replicated in high-quality, prospective studies; however, these findings brought forth the concept of ischemic preconditioning that has been demonstrated in other organs including the kidneys.

More recently, concern that the inverse may be true, that the administration of inhaled agents may be associated with neurotoxic effects was strongly supported by animal, including primate, models.²²³ These effects are the most reproducible at the extremes of age in animal models. A variety of potential mechanisms have been presented,²²⁴ with a demonstration of postexposure increases in neuronal and glial apoptosis associated with calcium dysregulation and many downstream effects in animal models.²²⁵⁻²²⁸ Behavior results in the elderly may include postoperative delirium and postoperative cognitive dysfunction that affects 20% to 40% of patients older than 60 years after anesthesia and surgery.²²⁹

Neurotoxicity in young children has been extensively studied by the SmartTots initiative and other groups.²³⁰ Early exposure to common anesthetic agents causes widespread neurodegeneration in the developing rat brain and persistent learning deficits.²²⁸ The widespread neuronal degeneration that results is thought to be a natural programmed response to synaptic silencing. Prolonged anesthesia with ketamine in neonatal monkeys (more than 9 hours) results in neuronal degeneration in the frontal cortex.²³¹ Whether normal exposures of young children to anesthesia for typical time periods could have neurodevelopmental effects has not been well supported by clinical studies. However, multiple large observational studies have suggested that multiple prolonged exposures to anesthesia may affect learning and development.²³²⁻²³⁷ These

concerns have led to a controversial U.S. Food and Drug Administration warning on anesthesia and brain development.²³⁸

Hepatic Effects

Hepatic Blood Flow

In patients receiving 1.5% end-tidal isoflurane, total hepatic blood flow and hepatic artery blood flow were maintained while portal vein blood flow was increased confirming that isoflurane was a vasodilator of the hepatic circulation providing beneficial effects on hepatic oxygen delivery.²³⁹ In contrast, halothane acts as a vasoconstrictor on the hepatic circulation. In another report, patients receiving 1 MAC isoflurane plus nitrous oxide demonstrated increases in hepatic blood flow and increased hepatic venous oxygen saturation, whereas hepatic blood flow did not change in patients receiving 1 MAC halothane plus nitrous oxide.²⁴⁰ Hepatic blood flow during administration of desflurane and sevoflurane is maintained similar to isoflurane in dogs (**Figure 4.49**).^{4,241} Maintenance of hepatic oxygen delivery relative to demand during exposure to anesthetics is uniquely important in view of the evidence that hepatocyte hypoxia is a significant mechanism in the multifactorial etiology of postoperative hepatic dysfunction.

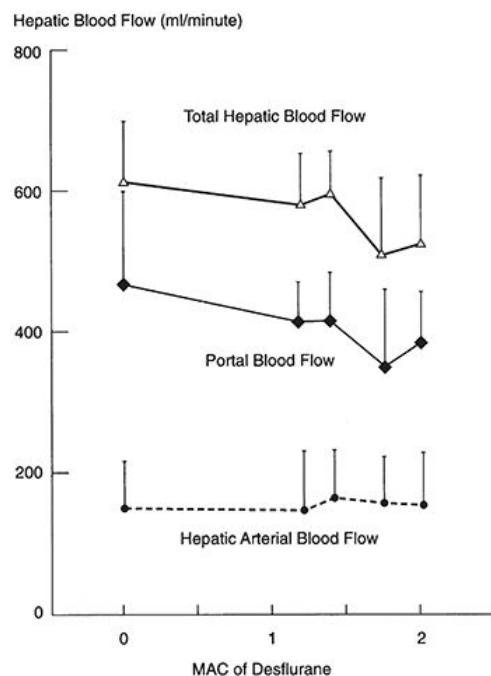


FIGURE 4.49 Administration of desflurane to dogs does not significantly alter hepatic perfusion. (Data are mean \pm standard deviation.) Derived from Eger EI. Desflurane (Suprane): A Compendium and Reference. Nutley, NJ: Anaquest; 1993:1-119.

Drug Clearance

Volatile anesthetics may interfere with clearance of drugs from the plasma. Intrinsic clearance by hepatic metabolism of drugs such as propranolol is decreased by 54% to 68% by inhaled anesthetics.²⁴² In the overall hepatic clearance of drugs anesthetic-induced inhibition of hepatic drug-metabolizing enzymes is most often implicated.²⁴³

Liver Function Tests

Transient increases in the plasma alanine aminotransferase activity follow administration of desflurane, but not isoflurane administration, to human volunteers (**Figure 4.50**).^{1,241} Transient increases in plasma concentrations of α -glutathione transferase (sensitive indicator of hepatocellular injury) follow administration

of isoflurane or desflurane for surgical anesthesia.²⁴⁴ In the presence of surgical stimulation, bromsulphalein retention and increases in liver enzymes follow transiently the administration of even isoflurane, suggesting that changes in hepatic blood flow evoked by painful stimulation can adversely alter hepatic function independent of the volatile anesthetic.

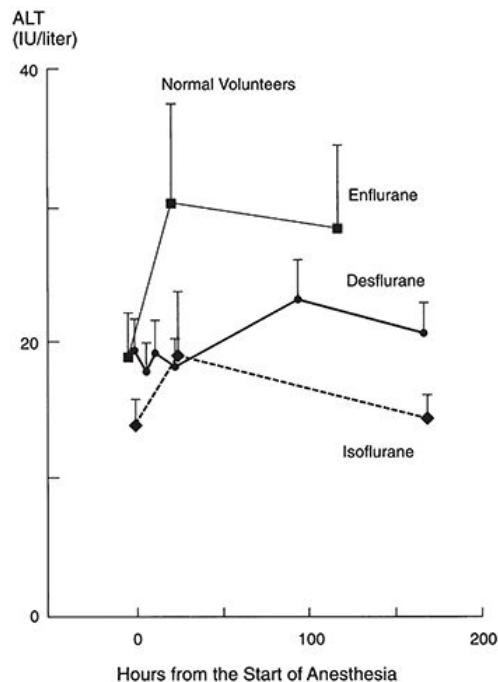


FIGURE 4.50 Plasma alanine aminotransferase (ALT) levels do not change significantly when enflurane, desflurane, or isoflurane are administered to healthy volunteers. (Data are mean \pm standard error.) Derived from Eger EI. Desflurane (Suprane): A Compendium and Reference. Nutley, NJ: Anaquest; 1993:1-119.

Hepatotoxicity

Postoperative liver dysfunction has been associated with most volatile anesthetics, but halothane has caused the most frequent and clinically relevant cases.²⁴⁵ Metabolism of halothane can produce free radicals that can alter hepatic proteins, creating antigens that stimulate the immune system.²⁴⁶ Preexisting liver disease, such as hepatic cirrhosis, may be associated with marginal hepatocyte oxygenation, which would be further jeopardized by the depressant effects of anesthetics on hepatic blood flow and/or arterial oxygenation. Hypothermia, which decreases hepatic oxygen demand, may protect the liver from drug-induced events that decrease hepatic oxygen delivery.

Halothane

Halothane produces two types of hepatotoxicity in susceptible patients. An estimated 20% of adult patients receiving halothane develop a mild, self-limited postoperative hepatotoxicity that is characterized by nausea, lethargy, fever, and minor increases in plasma concentrations of liver transaminase enzymes.²⁴⁷ The other and rarer type of hepatotoxicity (halothane hepatitis) is estimated to occur in 1 in 10,000 to 1 in 30,000 adult patients receiving halothane and may lead to massive hepatic necrosis and death.²⁴⁸ Children seem to be less susceptible to this type of hepatotoxicity than adults.^{249,250} It is likely that the more common self-limited form of hepatic dysfunction following halothane is a nonspecific drug effect due to changes in hepatic blood flow that impair hepatic oxygenation. Conversely, the rarer, life-threatening form of hepatic dysfunction characterized as halothane hepatitis is most likely an immune-mediated hepatotoxicity.²⁴⁵

Halothane Hepatitis

Clinical manifestations of halothane hepatitis that suggest an immune-mediated response include eosinophilia, fever, rash, arthralgia, and prior exposure to halothane. Risk factors commonly associated with halothane hepatitis include female gender, middle age, obesity, and multiple exposures to halothane. The predominant histologic feature is acute hepatitis. The most compelling evidence for an immune-mediated mechanism is the presence of circulatory immunoglobulin G antibodies in at least 70% of those patients with the diagnosis of halothane hepatitis.²⁴⁵ These antibodies are directed against liver microsomal proteins on the surface of hepatocytes that have been covalently modified by the reactive oxidative trifluoroacetyl halide metabolite of halothane to form neoantigens (Figure 4.51).²⁵¹ This acetylation of liver proteins in effect changes these proteins from self to nonself (neoantigens), resulting in the formation of antibodies against this new protein. It is presumed that the subsequent antigen-antibody interaction is responsible for the liver injury characterized as halothane hepatitis. The possibility of a genetic susceptibility factor is suggested by case reports of halothane hepatitis in closely related relatives.^{252,253} Indeed, metabolism of halothane appears to be under genetic influence in humans (Figure 4.52).²⁵⁴

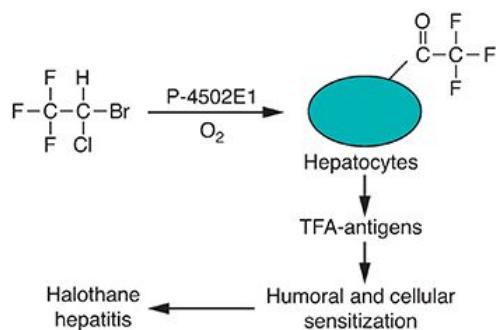


FIGURE 4.51 Halothane is metabolized to a trifluoroacetylated (TFA) adduct that binds to liver proteins. In susceptible patients, this adduct (altered protein) is seen as nonself (neoantigen), generating an immune response (production of antibodies). Subsequent exposure to halothane may result in hepatotoxicity. A similar process may occur in genetically susceptible individuals after anesthetic exposure to other fluorinated volatile anesthetics (enflurane, isoflurane, desflurane) that also generate a TFA adduct. *Reprinted with permission from Njoku D, Lesser MJ, Gong DH, et al. Biotransformation of halothane, enflurane, isoflurane, and desflurane to trifluoroacetylated liver proteins: association between protein acylation and hepatic injury. Anesth Analg. 1997;84(1):173-178. Copyright © 1997 International Anesthesia Research Society.*

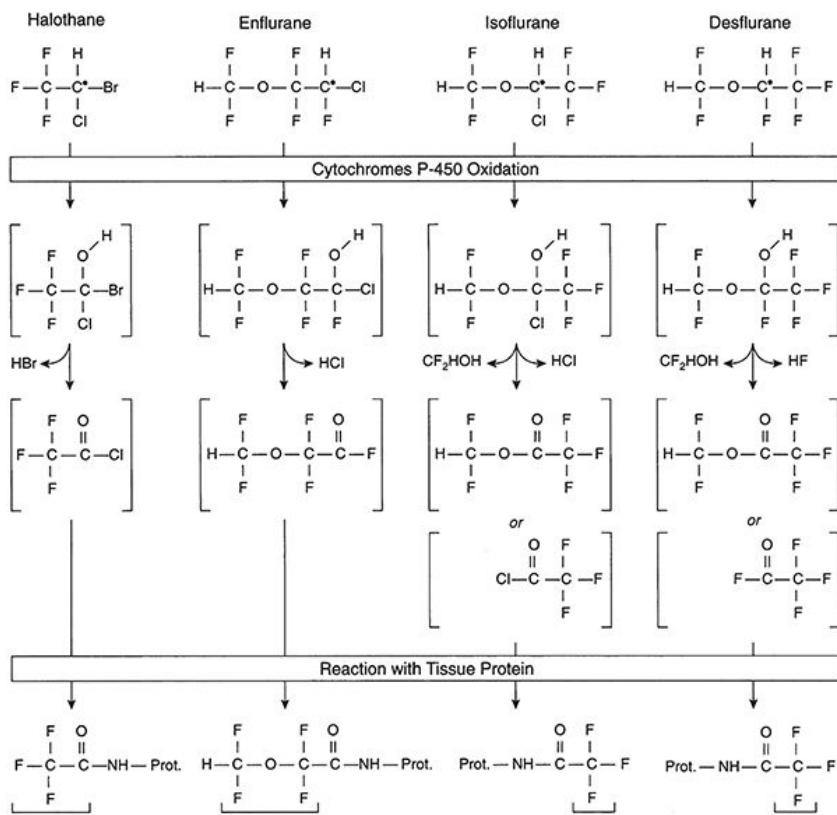


FIGURE 4.52 Pathways for the oxidative metabolism of fluorinated volatile anesthetics by cytochrome P450 enzymes to form acetylated protein adducts. In genetically susceptible individuals, the resulting trifluoroacetylates are thought to produce an immune response manifesting clinically as drug-induced hepatitis. *Reprinted with permission from Martin JL, Plevak DJ, Flannery KD, et al. Hepatotoxicity after desflurane anesthesia. Anesthesiology. 1995;83(5):1125-1129. Copyright © 1995 American Society of Anesthesiologists, Inc.*

Several observations suggest that reductive metabolism is not the primary mechanism in the development of halothane hepatitis. For example, neither enflurane nor isoflurane undergoes reductive metabolism; yet, these drugs both produce centrilobular necrosis in the hypoxic rat model. Furthermore, metabolites produced by reductive metabolism of halothane do not themselves produce hepatotoxicity. Finally, fasting does not alter metabolism but enhances hepatotoxicity by volatile anesthetics.

Enflurane, Isoflurane, and Desflurane

The mild, self-limited postoperative hepatic dysfunction that is associated with all the volatile anesthetics most likely reflect anesthetic-induced alterations in hepatic oxygen delivery relative to demand that results in inadequate hepatocyte oxygenation. More disturbing, however, is the realization that enflurane, isoflurane, and desflurane are oxidatively metabolized by liver cytochrome P450 enzymes to form acetylated liver protein adducts by mechanisms similar to that of halothane.²⁵¹⁻²⁵⁶ As a result, acetylated liver proteins capable of evoking an antibody response could occur after exposure to halothane, enflurane, isoflurane, or desflurane. Indeed, trifluoroacetyl-modified proteins have been described in a patient with hepatitis associated with isoflurane.²⁵⁷ This raises the possibility that enflurane, isoflurane, and desflurane could produce hepatotoxicity by a mechanism similar to that of halothane but at a lower incidence because the degree of anesthetic metabolism appears to be directly related to the potential for hepatic injury. Considering the magnitude of metabolism of these volatile anesthetics, it is predictable that the incidence of anesthetic-induced hepatitis would be greatest with halothane, intermediate with enflurane, and rare with isoflurane.²⁵⁸⁻
²⁶⁰ Desflurane is metabolized even less than isoflurane, and from the standpoint of immune-mediated

hepatotoxicity, desflurane should be very safe because it would have the lowest level of adduct formation. Nevertheless, even very small amounts of adduct may be able to precipitate massive hepatotoxicity, particularly if the patient was previously sensitized against trifluoroacetyl proteins. Indeed, hepatotoxicity after desflurane anesthesia has been described in a patient who may have been previously sensitized by exposure to halothane 18 and 12 years previously.²⁵⁶ Fulminant hepatic failure accompanied by high plasma concentrations of CYP2A6 autoantibodies has been observed in a patient 22 years following exposure to enflurane.²⁶¹ Similarly, halothane may be able to sensitize patients against protein adducts formed by other fluorinated volatile anesthetics.^{255,262}

The risk of fulminant hepatic failure after exposure to enflurane, isoflurane, or desflurane after previous exposure to halothane is probably less than the overall risk associated with anesthesia.²⁴⁵

Environmental exposure of operating room personnel to trace concentrations of volatile anesthetics could stimulate antibody production. Indeed, measurement of plasma autoantibody concentrations demonstrated increased levels in pediatric anesthesiologists (especially females) compared with general anesthesiologists and controls.²⁶³ It is presumed that pediatric anesthesiologists experience greater occupational exposure to trace concentrations of volatile anesthetics due to the frequent use of nonrebreathing anesthesia delivery systems and use of uncuffed endotracheal tubes. Despite these higher antibody levels, pediatric anesthesiologists did not have increased liver transaminase enzymes compared with general anesthesiologists, suggesting these antibodies may be insufficient to cause appreciable damage to normal hepatic cells.^{264,265}

Sevoflurane

The chemical structure of sevoflurane, unlike that of other fluorinated volatile anesthetics, dictates that it cannot undergo metabolism to an acetyl halide (**Figure 4.53**).^{266,267} Sevoflurane metabolism does not result in the formation of trifluoroacetylated liver proteins and therefore cannot stimulate the formation of antitrifluoroacetylated protein antibodies. In this regard, sevoflurane differs from halothane, enflurane, and desflurane, all of which are metabolized to reactive acetyl halide metabolites. Therefore, unlike all the other fluorinated volatile anesthetics, sevoflurane would not be expected to produce immune-mediated hepatotoxicity or to cause cross-sensitivity in patients previously exposed to halothane. Rare reported cases of sevoflurane hepatotoxicity are without explanation or proven cause and effect.^{4,268,269}

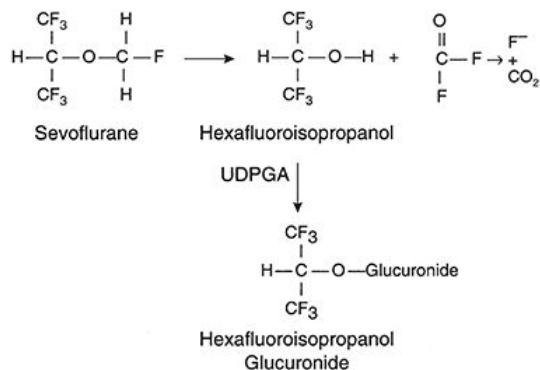


FIGURE 4.53 Proposed pathway for oxidative metabolism of sevoflurane. Abbreviation: UDPGA, uridine diphosphate glucuronic acid. Reprinted with permission from Frink EJ Jr, Ghantous H, Malan TP, et al. *Plasma inorganic fluoride with sevoflurane anesthesia: correlation with indices of hepatic and renal function.* Anesth Analg. 1992;74(2):231-235. Copyright © 1992 International Anesthesia Research Society.

Compound A, a product of sevoflurane interaction with carbon dioxide absorbents, is hepatotoxic in animals at above clinically relevant concentrations. Nevertheless, small increases in the plasma alanine aminotransferase have been observed in volunteers receiving sevoflurane for prolonged periods of time during which the compound A concentration averaged 41 ppm. Similar changes in the plasma transaminase concentrations did not occur in volunteers receiving desflurane, suggesting that mild transient hepatic injury

was limited to the sevoflurane-treated individuals.²⁷⁰ Conversely, others have not observed differences in liver function enzyme changes in patients receiving sevoflurane compared with isoflurane.²⁷¹

Renal Effects

Volatile anesthetics produce similar dose-related decreases in renal blood flow, glomerular filtration rate, and urine output. These changes are not a result of the release of arginine vasopressin hormone but rather most likely reflect the effects of volatile anesthetics on systemic blood pressure and cardiac output. Preoperative hydration attenuates or abolishes many of the changes in renal function associated with volatile anesthetics. Volatile anesthetics appear to induce a protective activity on the kidney similar to that of the heart due to antiinflammatory and antiapoptotic activity at least in preclinical studies.²⁷²

Fluoride-Induced Nephrotoxicity

Fluoride-induced nephrotoxicity (polyuria, hypernatremia, hyperosmolarity, increased plasma creatinine, inability to concentrate urine) was first recognized in patients after the administration of methoxyflurane, which undergoes extensive metabolism (70% of the absorbed dose) to inorganic fluoride, which acts as a renal toxin. The methoxyflurane nephrotoxicity theory had been extended to other fluorinated volatile anesthetics despite the absence of data to support this extrapolation. As earlier, current studies suggest that newer volatile anesthetics may be protective against acute kidney injury.

Sevoflurane

Prolonged sevoflurane anesthesia does not impair renal concentrating function as evaluated with desmopressin testing 1 and 5 days postanesthesia in healthy volunteers.^{273,274}

Despite reports failing to show renal impairment after the administration of sevoflurane, there are observations of transient impairment of renal concentrating ability and increased urinary excretion of β -N-acetylglucosaminidase in patients exposed to sevoflurane and developing peak plasma inorganic fluoride concentrations $>50 \mu\text{mol/L}$ (**Figures 4.54** and **4.55**).²⁷⁵ Urinary excretion of β -N-acetylglucosaminidase is considered an indicator of acute proximal renal tubular injury. Despite these changes, the blood urea nitrogen and plasma creatinine did not change, and the authors concluded that clinically significant renal damage did not accompany administration of sevoflurane to patients with no preexisting renal disease. Concern that administration of sevoflurane to patients with preexisting renal disease could accentuate renal dysfunction was not confirmed when this volatile anesthetic was administered to patients with chronic renal disease as reflected by increased plasma creatinine concentrations.^{273,276} Likewise, administration of desflurane or isoflurane did not aggravate renal impairment in patients with preexisting chronic renal insufficiency (**Figure 4.56**).²⁷⁷

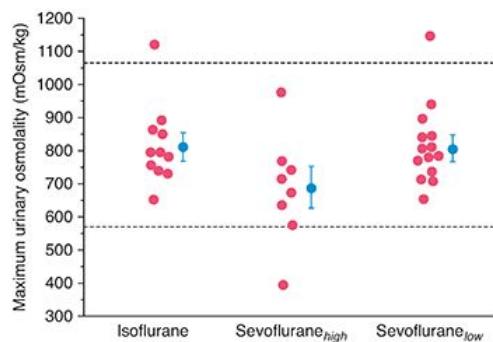


FIGURE 4.54 Maximum urinary osmolality in response to vasopressin 16.5 hours after cessation of anesthesia was not significantly different between the three anesthesia groups. Sevoflurane_{high} included only patients with a peak plasma inorganic fluoride concentration $>50 \mu\text{mol/L}$. Solid circles and bars represent mean \pm standard error. Reprinted with permission from Higuchi H, Sumikura H, Sumita S, et al. Renal function in patients with high serum fluoride concentrations after prolonged sevoflurane anesthesia. *Anesthesiology*. 1995;83(3):449-458. Copyright © 1995 American Society of Anesthesiologists, Inc.

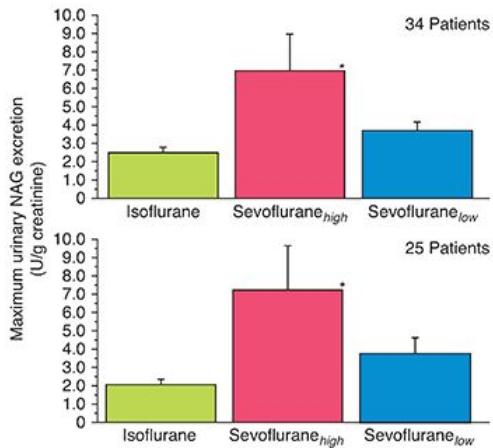


FIGURE 4.55 Urinary excretion of the renal enzyme β -N-acetylglucosaminidase (NAG) was significantly greater (* $P < .05$) in the sevoflurane-high patients (peak plasma inorganic fluoride concentration >50 microns per liter) compared with the other anesthesia groups. Reprinted with permission from Higuchi H, Sumikura H, Sumita S, et al. Renal function in patients with high serum fluoride concentrations after prolonged sevoflurane anesthesia. *Anesthesiology*. 1995;83(3):449-458. Copyright © 1995 American Society of Anesthesiologists, Inc.

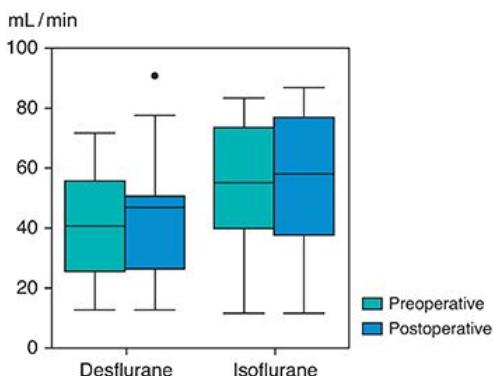


FIGURE 4.56 Preoperative and postoperative creatinine clearance values (mL/min). Thick lines represent median values, the box boundaries represent 25th to 75th percentiles, and the bar lines represent the 10th to 90th percentiles. The single outlier beyond the 90th percentile is shown as an individual data point (asterisk). There were no differences between desflurane and isoflurane. Reprinted with permission from Litz RJ, Hübner M, Lorenz W, et al. Renal responses to desflurane and isoflurane in patients with renal insufficiency. *Anesthesiology*. 2002;97(5):1133-1136. Copyright © 2002 American Society of Anesthesiologists, Inc.

It has been postulated that intrarenal production of inorganic fluoride may be a more important factor for nephrotoxicity than hepatic metabolism that causes increased plasma fluoride concentrations.^{266,278} This would explain why patients with increased plasma concentrations of fluoride after administration of sevoflurane occasionally experience less renal dysfunction than patients receiving enflurane and manifesting lower plasma fluoride concentrations.^{273,274,279} Presumably, inhaled anesthetics such as methoxyflurane and enflurane undergo greater intrarenal metabolism to fluoride than sevoflurane, whereas sevoflurane undergoes greater hepatic metabolism, thus accounting for the higher plasma concentrations of fluoride.

Vinyl Halide Nephrotoxicity

Carbon dioxide absorbents containing potassium and sodium hydroxide react with sevoflurane and eliminate hydrogen fluoride from its isopropyl moiety to form breakdown products (**Figure 4.57**).^{5,280} The degradation product produced in greatest amounts is fluoromethyl-2,2-difluoro-1-(trifluoromethyl)vinyl ether (compound A). During closed-circuit anesthesia with sevoflurane administered to patients undergoing operations lasting longer than 5 hours, the average concentration of compound A in the anesthesia circuit was <20 ppm and no evidence of renal dysfunction occurred based on measurements of blood urea nitrogen and plasma creatinine concentrations (**Figure 4.58**).²⁴ Higher concentrations of compound A occurred in the presence of Baralyme (no longer clinically available) probably as a result of higher absorbent temperatures compared with soda lime.^{5,104} Similarly, carbon dioxide production increases the absorbent temperature and thus the production of compound A.

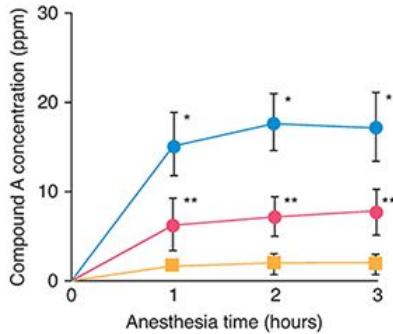


FIGURE 4.57 Inhaled compound A concentrations during administration of sevoflurane at fresh gas flow rates of 1 L per minute (blue circles), 3 L per minute (red circles), and 6 L per minute (squares) (* $P < .05$ vs 3 L per minute; ** $P < .05$ vs 6 L per minute). *Reprinted from Bito H, Ikeda K. Effect of total flow rate on the concentration of degradation products generated by reaction between sevoflurane and soda lime. Br J Anaesth. 1995;74(6):667-669. Copyright © 1995 Elsevier. With permission.*

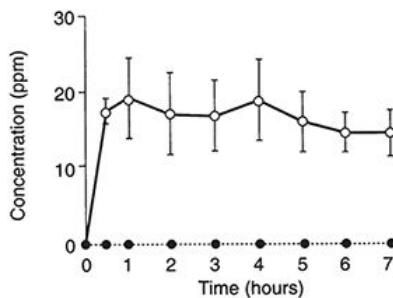


FIGURE 4.58 Inhaled compound A concentrations (open circles) and compound B concentrations (solid circles) during closed-circuit sevoflurane anesthesia. (Data are mean \pm standard deviation.) *Reprinted with permission from Bito H, Ikeda K. Closed-circuit anesthesia with sevoflurane in humans: effects of renal and hepatic function and concentrations of breakdown products with soda lime in the circuit. Anesthesiology. 1994;80(1):71-76. Copyright © 1994 American Society of Anesthesiologists, Inc.*

The rationale for the limitation of gas flow to at least 2 L per minute when administering sevoflurane is intended to minimize the concentration of compound A that may accumulate in the anesthesia breathing circuit. To assess the adequacy of this recommendation, the nephrotoxicity of 2, 4, or 8 hours of anesthesia with 1.25 MAC sevoflurane has been compared with a similar exposure to desflurane.^{270,281} Compound A concentrations ranged from 40 to 42 ppm during the three different durations of sevoflurane administration. In patients receiving 1.25 MAC sevoflurane for 8 hours or 4 hours, there was transient evidence of injury to the glomeruli (albuminuria), proximal renal tubules (glucosuria and increased urinary excretion of glutathione-S-transferase), and distal renal tubules (increased urinary excretion of glutathione-S-transferase) that was greater in the 8-hour group. Urine-concentrating ability and plasma creatinine were not altered

despite these findings in the patients receiving sevoflurane. Desflurane administered at 1.25 MAC for 2, 4, or 8 hours or sevoflurane exposure for 2 hours did not produce any evidence of renal injury. Conversely, comparisons of the renal effects of sevoflurane and isoflurane using fresh gas flows of 1 L per minute or less demonstrated no difference between these drugs based on measurement of indices of renal function.²⁸²⁻²⁸³ In children, sevoflurane anesthesia lasting 4 hours using total fresh gas flows of 2 L per minute produced concentrations of compound A of <15 ppm, and there was no evidence of renal dysfunction.²⁸⁴

Skeletal Muscle Effects

Neuromuscular Junction

Volatile anesthetics inhibit muscle type nicotinic receptors incompletely at MACs.²⁸⁵ Ether derivative fluorinated volatile anesthetics (isoflurane, sevoflurane, and desflurane) produce skeletal muscle relaxation that is about twofold greater than that associated with a comparable dose of halothane. Nitrous oxide does not relax skeletal muscles, and in doses of >1 MAC (delivered in a hyperbaric chamber), it may produce skeletal muscle rigidity.¹⁶³ This is not clinically relevant except perhaps in hyperbaric medicine. This effect of nitrous oxide is consistent with enhancement of skeletal muscle rigidity produced by opioids when low concentrations of nitrous oxide are administered. The ability of skeletal muscles to sustain contractions in response to continuous stimulation (such as with a nerve muscle stimulator) is impaired in the presence of increasing concentrations of ether derivative volatile anesthetics but not in the presence of halothane or nitrous oxide ([Figure 4.59](#)).¹

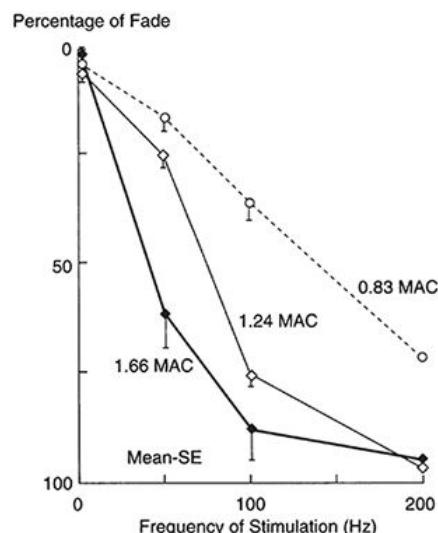


FIGURE 4.59 Increases in fade with tetanic stimulation accompany increasing doses of desflurane or increasing frequency of stimulation. Abbreviations: MAC, minimal alveolar concentration; SE, standard error. *Derived from Eger EI. Desflurane (Suprane): A Compendium and Reference. Nutley, NJ: Anaquest; 1993:1-119.*

Volatile anesthetics produce dose-dependent enhancement of the effects of neuromuscular-blocking drugs, with the effects of isoflurane, desflurane, and sevoflurane being similar and greater than halothane. In vitro, isoflurane and halothane produce similar potentiation of the effects of neuromuscular-blocking drugs.²⁸⁶ Nitrous oxide does not significantly potentiate the in vivo effects of neuromuscular-blocking drugs.

Malignant Hyperthermia

All volatile anesthetics including desflurane and sevoflurane can trigger malignant hyperthermia in genetically susceptible patients even in the absence of concomitant administration of succinylcholine.²⁸⁷⁻²⁸⁹ In one report, malignant hyperthermia did not manifest until 3 hours following uneventful desflurane anesthesia.²⁹⁰ Among the volatile anesthetics, however, halothane is the most potent trigger. Despite previous

data from animal models, nitrous oxide does not trigger malignant hyperthermia in humans. Xenon²⁹¹ can also be given safely to a patient with a history of malignant hyperthermia, although current anesthesia machines need longer flushing times than earlier simpler machines and manufacturer's instructions should be followed. Malignant Hyperthermia Association of the United States (MHAUS) is a nonprofit organization designed to promote best practices and scientific understanding of malignant hyperthermia. It currently runs a hotline for emergency recommendations for health care professionals in the management of an acute suspected case of malignant hyperthermia.²⁹²

Obstetric Effects

Volatile anesthetics produce similar and dose-dependent decreases in uterine smooth muscle contractility and blood flow (**Figure 4.60**).^{127,293,294} These changes are modest at 0.5 MAC (analgesic concentrations) and become substantial at concentrations of >1 MAC as such, nitrous oxide is particularly useful in obstetrical anesthesia to reduce the need to volatile anesthetic that promotes uterine atony while avoiding opioids and benzodiazepines that may cause prolonged depression of the newborn.

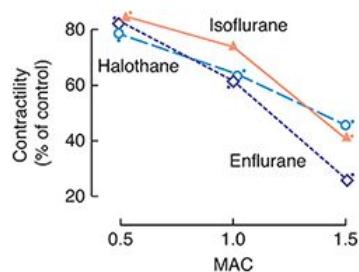


FIGURE 4.60 Impact of volatile anesthetics on contractility of uterine smooth muscle strips studied in vitro (*P > .05). Abbreviation: MAC, minimal alveolar concentration. *Reprinted with permission from Eger EI. Isoflurane (Forane): A Compendium and Reference. Madison, WI: Ohio Medical Products; 1981:1-110.*

In some settings, anesthetic-induced uterine relaxation may be desirable to facilitate removal of retained placenta; nitroglycerine can also be used for this purpose. Conversely, uterine relaxation produced by volatile anesthetics may contribute to blood loss due to uterine atony. Indeed, blood loss during therapeutic abortion is greater in patients anesthetized with a volatile anesthetic compared with that in patients receiving propofol.^{295,296} Propofol inhibits uterine contractility only slightly at anesthetic concentrations.²⁹⁷

There is a higher risk of awareness in women undergoing cesarean section compared to those who undergo other general surgery.²⁹⁸ Volatile anesthetics at about 0.5 MACs combined with 50% nitrous oxide provide a reasonable assurance of amnesia during cesarean section and do not produce detectable effects in the neonate.²⁹⁹ However, remember that MAC is defined as the concentration of an inhaled anesthetic that prevents movement in 50% of patients. Clearly, a 50% incidence of memory under general anesthesia is unacceptable! One MAC of an anesthetic is more reasonable, as the concentration of volatile anesthetic required for amnesia is approximately one-third of that required to prevent movement and dose response curves are very steep putting the likelihood of awareness during cesarean section considerably lower than 50%.³⁰⁰⁻³⁰² Another consideration is that MAC is thought to be primarily due to inhibition of a spinal reflex.⁶⁶ Awareness clearly requires a supratentorial contribution. When possible, absence of movement in response to surgical stimulus while avoiding muscle relaxation after intubation provides some assurance that at least a MAC is being used.

Inhaled anesthetics rapidly cross the placenta to enter the fetus, but these drugs are likewise rapidly exhaled by the newborn infant. Nitrous oxide-induced analgesia for vaginal delivery develops more rapidly than with most volatile anesthetics (desflurane and sevoflurane may be exceptions), but, after about 10 minutes, all inhaled drugs provide comparable analgesia. It is not known over what period of time the analgesic properties recover. These topics are discussed more fully in [Chapter 45](#).

Resistance to Infection

Many normal functions of the immune system are depressed after patient exposure to the combination of anesthesia and surgery.³⁰³ It would seem that many of the immune changes seen in surgical patients are primarily the result of surgical trauma and the subsequent endocrine (catecholamines and corticosteroids) and inflammatory responses (cytokines and chemokines) rather than the result of the anesthetic exposure itself. However, inhaled anesthetics, particularly nitrous oxide, produce dose-dependent inhibition of polymorphonuclear leukocytes and their subsequent migration (chemotaxis) for phagocytosis, which is necessary for the inflammatory response to infection. Nevertheless, decreased resistance to bacterial infection due to inhaled anesthetics seems unlikely, considering the duration of administration and dose of these drugs. Furthermore, when leukocytes reach the site of infection, their ability to phagocytize bacteria appears to be normal. Inhaled anesthetics do not have bacteriostatic effects at clinically used concentrations.

Genetic Effects

The Ames test, which identifies chemicals that act as mutagens and carcinogens, is negative for isoflurane, desflurane, sevoflurane, and nitrous oxide, and their known metabolites.^{23,304,305} Compound A, which is formed from sevoflurane degradation by carbon dioxide absorbents, might be expected to be an alkylating agent (and thus a mutagen), but tests of this product do not reveal mutagenicity.³⁰⁶ Halothane also results in a negative Ames test, but some of its potential metabolites may be positive.³⁰⁷

Nitrous oxide irreversibly oxidizes the cobalt atom of vitamin B₁₂ such that the activity of vitamin B₁₂-dependent enzymes (methionine synthetase and thymidylate synthetase) is decreased. In patients undergoing laparotomy with general anesthesia including 70% nitrous oxide, the half-time for inactivation of methionine synthetase is about 46 minutes (**Figure 4.61**).³⁰⁸ Volatile anesthetics do not alter activity of vitamin B₁₂-dependent enzymes.

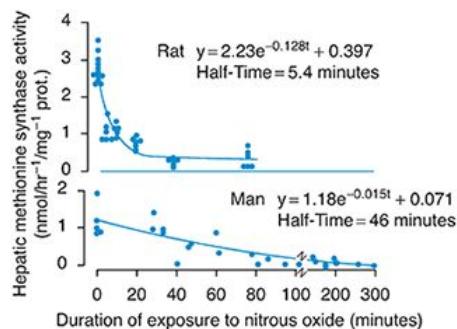


FIGURE 4.61 Time course of inactivation of hepatic methionine synthase (synthetase) activity during administration of 50% nitrous oxide to rats or 70% nitrous oxide to humans. Reprinted with permission from Royston BD, Nunn JF, Weinbren HK, et al. Rate of inactivation of human and rodent hepatic methionine synthase by nitrous oxide. Anesthesiology. 1988;68(2):213-216. Copyright © 1988 American Society of Anesthesiologists, Inc.

A 1995 trial designed to evaluate the effect of nitrous oxide among dental assistants on the rate of spontaneous abortion found a relative risk of 2.6 in women who worked with nitrous oxide for more than 3 hours a week without scavenging equipment, whereas the risk was not elevated among women working in offices that used scavenging equipment.³⁰⁹ The speculated role of trace concentrations of nitrous oxide in the production of spontaneous abortions led to the use of scavenging systems designed to remove waste anesthetic gases, including nitrous oxide, from the ambient air of the operating room. Health care workers exposed to nitrous oxide have lower levels of vitamin B₁₂ in proportion to their exposure.³¹⁰ Methionine synthetase converts homocysteine to methionine, which is necessary for the formation of myelin. Thymidylate synthetase is important for DNA synthesis. Interference with myelin formation and DNA synthesis could have significant effects on the rapidly growing fetus, manifesting as spontaneous abortions or congenital anomalies. Inhibition of these enzymes could also manifest as depression of bone marrow function and neurologic disturbances. Women do not normally choose to have elective surgery during the first

trimester of pregnancy when the risk is highest for spontaneous abortion. As discussed earlier, in animal models, all general anesthetics with the exception of Xenon that readily available cause neuroapoptosis in animals and there is no evidence that one is worse than the other. The lowest safe anesthetic doses for the shortest period of time are recommended for urgent surgery during the first trimester.³¹¹

Bone Marrow Function

Interference with DNA synthesis is responsible for the megaloblastic changes and agranulocytosis that may follow prolonged administration of nitrous oxide. Megaloblastic changes in bone marrow are consistently found in patients who have been exposed to anesthetic concentrations of nitrous oxide for 24 hours.³¹² Exposure to nitrous oxide lasting 4 days or longer results in agranulocytosis. This is not a common clinical occurrence. These bone marrow effects occur as a result of nitrous oxide–induced interference with activity of vitamin B₁₂–dependent enzymes, which are necessary for synthesis of DNA and the subsequent formation of erythrocytes (see the section “[Genetic Effects](#)”). Despite these potential adverse effects on bone marrow function, the administration of nitrous oxide to patients undergoing bone marrow transplantation does not influence bone marrow viability ([Figure 4.62](#)).³¹³

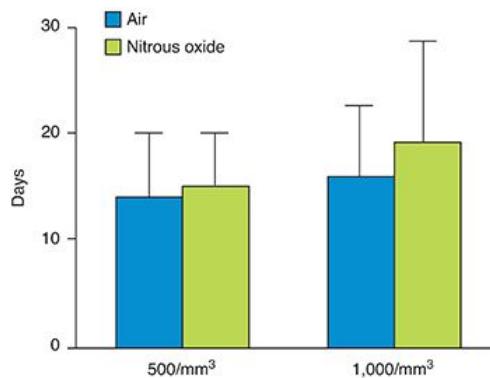


FIGURE 4.62 Nitrous oxide administered during bone marrow harvest did not alter the subsequent number of days needed for cultures to grow 500 to 1,000 cells/mm³. (Data are mean \pm standard deviation.) Reprinted with permission from Lederhaas G, Brock-Utne JG, Negrin RS, et al. Is nitrous oxide safe for bone marrow harvest? *Anesth Analg*. 1995;80(4):770-772. Copyright © 1995 International Anesthesia Research Society.

It is presumed that a healthy surgical patient could receive nitrous oxide for 24 hours without harm. Because the inhibition of methionine synthetase is rapid and its recovery is slow, it is to be expected that repeated exposures at intervals of <3 days may result in a cumulative effect. This relationship may be further complicated by other factors influencing levels of methionine synthetase and tetrahydrofolate (necessary for the transmethylation reaction) that might be important in critically ill patients receiving nitrous oxide. Nevertheless, the contradiction between the serious biochemical effects of nitrous oxide and the apparent absence of adverse clinical effects in routine use of this inhaled anesthetic makes it difficult to draw firm conclusions.

Peripheral Neuropathy

Animals exposed to 15% nitrous oxide for up to 15 days develop ataxia and exhibit evidence of spinal cord and peripheral nerve degeneration. Humans who chronically inhale nitrous oxide for nonmedical purposes may develop a neuropathy characterized by sensorimotor polyneuropathy that is often combined with signs of posterior lateral spinal cord degeneration resembling pernicious anemia.³¹⁴ The speculated mechanism of this neuropathy is the ability of nitrous oxide to oxidize irreversibly the cobalt atom of vitamin B₁₂ such that activity of vitamin B₁₂–dependent enzymes is decreased (see the section “[Genetic Effects](#)”).

Total Body Oxygen Requirements

Total body oxygen requirements are decreased by similar amounts by different volatile anesthetics. The oxygen requirements of the heart decrease more than those of other organs, reflecting drug-induced decreases in cardiac work associated with decreases in systemic blood pressure and myocardial contractility. Therefore, decreased oxygen requirements would protect tissues from ischemia that might result from decreased oxygen delivery due to drug-induced decreases in perfusion pressure. Decreases in total body oxygen requirements probably reflect metabolic depressant effects as well as decreased functional needs in the presence of anesthetic-produced depression of organ function.

Metabolism

Metabolism of modern drugs does not significantly affect either the onset or offset of drug effect. Based on mass balance studies, it is concluded that alveolar ventilation is principally responsible for the elimination of enflurane and isoflurane (presumably also desflurane and sevoflurane). Metabolism plays an important role for elimination of halothane that increases the risk for halothane hepatitis in susceptible individuals.^{315,316}

Environmental Impact of Inhaled Anesthetics

Greenhouse gases absorb and emit thermal radiation. They trap reflected sunlight and other terrestrial sources of infrared radiation within the atmosphere. A greenhouse gas must be present in sufficient quantities to potentially alter the equilibration between radiant energy absorbed from the sun and radiant energy dissipated into space from the Earth. The most important greenhouse gas, carbon dioxide, is taken up by plants and potentially by chemical reactions that can capture carbon dioxide. Most other greenhouse gases linger in the atmosphere for years (**Table 4.9**). This combination allows for the interference with the escape of such radiation from the earth's lower atmosphere. The resultant absorption of such radiant energy rather than its free release into space contributes to the "greenhouse effect": the process by which atmospheric radiation progressively warms the surface and lower atmosphere of the planet.

TABLE 4.9

Atmospheric lifetimes, radiative efficiencies, ozone depletion potentials, and global warming potentials of inhaled anesthetics^a

Compound	AL (years)	RE (W m^{-2} ppb $^{-1}$)	ODP	GWP ₂₀	GWP ₁₀₀
Nitrous oxide (N ₂ O)	114	0.00303	0.017	289	298
Halothane (CF ₃ CHBrCl)	1.0	0.165	0.4	190	50
Enflurane (CHFCICF ₂ OCF ₂ H)	4.3	0.447	0.01	2370	680
Isoflurane (CHF ₂ OCHClCF ₃)	3.2	0.453	0.01	1800	510
Desflurane (CHF ₂ OCHFCF ₃)	14	0.469	0	6810	2540
Sevoflurane ([CF ₃] ₂ CHOCH ₂ F)	1.1	0.351	0	440	130

Abbreviations: AL, atmospheric lifetime; GWP₂₀, global warming potential for 20 years; GWP₁₀₀, global warming potential for 100 years; ODP, ozone depletion potential; RE, radiative efficiency.

^aData adapted from Sulbaek Andersen MP, Nielsen OJ, Wallington TJ, et al. Assessing the impact of global climate from general anesthetic gases. *Anesth Analg*. 2012;114:1081-1085.

All inhaled anesthetics are well-documented contributors to the greenhouse effect. Additionally, many of the inhaled anesthetics are known to deplete the stratospheric ozone layer as well. Specifically, isoflurane, enflurane, and halothane are known to participate in the chlorine-mediated catalytic destruction of the ozone layer. Desflurane and sevoflurane are known to produce CF₃O₂ radicals, although they are not associated with direct ozone destruction.³¹⁷ Nitrous oxide is a prominent contributor to both ozone destruction as well as the greenhouse effect.³¹⁸

To evaluate the relative potential contribution of a particular greenhouse gas to climate change, the global warming potential has been developed. The global warming potential is the ratio of time-integrated

radiative efficiency and the atmospheric lifetime of a forcing agent, relative to a reference gas (eg, carbon dioxide). In comparing global warming potentials, clinical equivalences have been referenced in relation to automotive emissions.³¹⁹ In a single 8-hour day of anesthetic usage, desflurane run at 1 to 2 L of fresh gas flow produces 58 to 116 days' worth of average auto emissions. Sevoflurane (2 L fresh gas flow) and isoflurane (1-2 L fresh gas flow) produce the equivalents of 4.3 and 4.8 to 9.6 days of average auto emissions, respectively. When all are used at 2 L fresh gas flow, desflurane demonstrates roughly 26 and 13 times the global warming potential of sevoflurane and isoflurane, respectively. Furthermore, the vaporization of a single bottle of desflurane produces the same global warming effect as 886 kg of carbon dioxide (**Table 4.9**).³²⁰

Proposed mechanisms for limiting the environmental impact of inhalational agents include closed-circuit anesthetics, low-flow administration of the less environmentally detrimental inhalational agents, and total intravenous anesthetic techniques. The use of propofol in place of inhalational agents, for example, was demonstrated to produce nearly four orders of magnitude less greenhouse gas than nitrous or desflurane. Of note, the greenhouse gas effects of propofol result specifically from energy requirements for medication administration (ie, operation of pump systems) rather than environmental release of the medication.³²¹

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Intravenous Sedatives and Hypnotics*

Updated by: James P. Rathmell • Albert Dahan

Overview

No other class of pharmacologic agents is more central to the practice of anesthesiology than the intravenous (IV) sedatives and hypnotics. It is this group of agents that we rely upon to provide everything through the spectrum from anxiolysis to light and deep sedation all the way to general anesthesia. The term **sedative** refers to a drug that induces a state of calm or sleep. The term **hypnotic** refers to drug that induces hypnosis or sleep. There is significant overlap in the two terms as well as with the related term **anxiolytic**, which refers to any agent that reduces anxiety; nearly all such substances have sedation as a side effect. For practical purposes, we generally combine the terms and refer to all of these drugs as **sedative-hypnotics**, drugs that reversibly depress the activity of the central nervous system (CNS). Depending on the specific agent, the dose, and the rate of administration, many sedative-hypnotics can be used to allay anxiety with minimal sedation, produce varying degrees of sedation, or rapidly induce drug-induced unconsciousness, which we call **general anesthesia**. We review the pharmacology of these important agents in this chapter.

γ -Aminobutyric Acid Agonists

Propofol

Propofol is a substituted isopropylphenol (2,6-diisopropylphenol) that is administered intravenously as a 1% solution in an aqueous solution of 10% soybean oil, 2.25% glycerol, and 1.2% purified egg phosphatide.¹⁻³ This drug is chemically distinct from all other drugs that act as IV sedative-hypnotics. Administration of propofol, 1.5 to 2.5 mg/kg IV (equivalent to thiopental, 4-5 mg/kg IV, or methohexitol, 1.5 mg/kg IV) as a rapid IV injection (<15 seconds), produces unconsciousness within about 30 seconds. Awakening is more rapid and complete than that after induction of anesthesia with all other drugs used for rapid IV induction of anesthesia. The more rapid return of consciousness with minimal residual CNS effects is one of the most important advantages of propofol compared with alternative drugs administered for the same purpose.

Commercial Preparations

Propofol is an insoluble drug that requires a lipid vehicle for emulsification. Soybean oil holds the propofol in a medium that can be stabilized and dispersed; lecithin serves as an emulsifier to stabilize the small propofol–soybean oil droplets in aqueous dispersion, and glycerol maintains the formulation isotonic with blood.^{4,5} This formulation supports bacterial growth and causes increased plasma triglyceride concentrations when prolonged IV infusions are used. Diprivan and generic propofol differ with respect to the preservatives used and the pH of the formulation. Diprivan uses the preservative disodium edetate (0.005%) with sodium hydroxide to adjust the pH to 7 to 8.5. A generic formulation of propofol incorporates sodium metabisulfite (0.25 mg/mL) as the preservative and has a lower pH (4.5-6.4). Propofol, unlike thiopental, etomidate, and ketamine, is not a chiral compound. The mixing of propofol with any other drug is not recommended, although lidocaine has been frequently added to propofol in attempts to prevent pain with IV injection. However, mixing of lidocaine with propofol may result in coalescence of oil droplets, which may pose the risk of pulmonary embolism.⁶

A low-lipid emulsion of propofol (Ampofol) contains 5% soybean oil and 0.6% egg lecithin but does not require a preservative or microbial growth retardant.⁷ This formulation is equipotent to Diprivan but is associated with a higher incidence of pain on injection.

An alternative to emulsion formulations of propofol and associated side effects (pain on injection, risk of infection, hypertriglyceridemia, pulmonary embolism) is creation of a prodrug (Aquavan, fospropofol) by cleaving groups to the parent compound that increase its water solubility (phosphate monoesters, hemisuccinates). Propofol is liberated after hydrolysis by endothelial cell surface alkaline phosphatases. In

this regard, injection of the water-soluble propofol phosphate prodrug results in propofol and dose-dependent sedative effects.^{8,9} However, although the absence of lipid emulsion obviates pain on injection, the release of a small amount of formaldehyde byproduct causes an unpleasant dysesthesia or burning sensation often in the perineal area. Compared with propofol, this prodrug has a slower onset, larger volume of distribution (V_d), and higher potency.¹⁰ This drug was under active development in the late 2000s; publication of phase I and phase II clinical results were retracted in 2010 due to inaccuracies with the assays used and further development was halted.¹¹

Another nonlipid formulation of propofol uses cyclodextrins as a solubilizing agent.^{12,13} Cyclodextrins are ring sugar molecules that form guest (propofol)-host complexes migrating between the hydrophilic center of the cyclodextrin molecule and the water-soluble phase. This allows propofol, which is poorly soluble in water, to be presented in an injectable form. After injection, propofol migrates out of the cyclodextrin into the blood. This preparation has not been released for general human use.

Mechanism of Action

Propofol is a relatively selective modulator of γ -aminobutyric acid type A ($GABA_A$) receptors. Propofol is presumed to exert its sedative-hypnotic effects through a $GABA_A$ receptor interaction, although potentiation of activity at glycine receptors partially contributes to propofol-induced hypnosis.^{14,15} The $GABA$ is the principal inhibitory neurotransmitter in the brain. When $GABA_A$ receptors are activated, transmembrane chloride conductance increases, resulting in hyperpolarization of the postsynaptic cell membrane and functional inhibition of the postsynaptic neuron. The interaction of propofol (also etomidate and barbiturates) with specific components of $GABA_A$ receptors appears to decrease the rate of dissociation of the inhibitory neurotransmitter $GABA$ from the receptor, thereby increasing the duration of the $GABA$ -activated opening of the chloride channel with resulting hyperpolarization of cell membranes. In contrast to volatile anesthetics, spinal motor neuron excitability, as measured by H reflexes, is not altered by propofol, suggesting that immobility during propofol anesthesia is not caused by drug-induced spinal cord depression.¹⁶

Pharmacokinetics

Clearance of propofol from the plasma exceeds hepatic blood flow, emphasizing that tissue uptake (possibly into the lungs), as well as hepatic oxidative metabolism by cytochrome P450, is important in removal of this drug from the plasma (Figure 5.1) (Table 5.1).¹⁷ Hepatic metabolism is rapid and extensive, resulting in inactive, water-soluble sulfate and glucuronic acid metabolites that are excreted by the kidneys.¹⁸ Propofol may also undergo ring hydroxylation by cytochrome P450 to form 4-hydroxypropofol which is then glucuronidated or sulfated. Although the glucuronide and sulfate conjugates of propofol appear to be pharmacologically inactive, 4-hydroxypropofol has about one-third the hypnotic activity of propofol. Less than 0.3% of a dose is excreted unchanged in urine. The elimination half-time is 0.5 to 1.5 hours, but more important, the context-sensitive half-time for propofol infusions lasting up to 8 hours is less than 40 minutes.¹⁹ The context-sensitive half-time of propofol is only minimally influenced by the duration of the infusion at surgical durations (hours) relevant for most surgery. When the infusion is discontinued, drug returns from tissue storage sites to the circulation. Once in the circulation, propofol is rapidly metabolized and cleared, and little of the drug is available to slow the decline in plasma concentration. However, when used as a sedative for prolonged intensive care unit (ICU) care (days), the context-sensitive half-time becomes highly relevant and may lead to prolonged effects when the drug is discontinued. Propofol, like thiopental and remifentanil, has a short effect-site equilibration time such that effects on the brain occur promptly after IV administration.

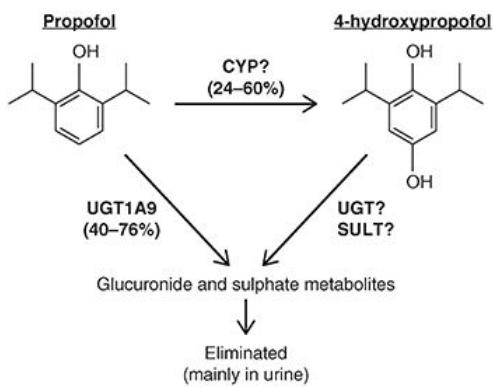


FIGURE 5.1 Major metabolic pathways for propofol. Reprinted with permission from Court MH, Duan SX, Hesse LM, et al. Cytochrome P-450 2B6 is responsible for interindividual variability of propofol hydroxylation by human liver microsomes. *Anesthesiology*. 2001;94(1):110-119. Copyright © 2001 American Society of Anesthesiologists, Inc.

TABLE 5.1

Comparative characteristics of common induction drugs

	Elimination half-time (hour)	Volume of distribution (L/kg)	Clearance (mL/kg/minute)	Systemic blood pressure	Heart rate
Propofol	0.5-1.5	3.5-4.5	30-60	Decreased	Decreased
Etomidate	2-5	2.2-4.5	10-20	No change to decreased	No change
Ketamine	2-3	2.5-3.5	16-18	Increased	Increased

The fact that total body clearance of propofol exceeds hepatic blood flow is consistent with extrahepatic clearance (pulmonary uptake and first-pass elimination, renal excretion) of propofol.¹⁸⁻²⁰ Pulmonary uptake of propofol is significant and influences the initial availability of propofol. Although propofol can be transformed in the lungs to 2,6-diisopropyl-1,4-quinol, most of the drug that undergoes pulmonary uptake during the first pass is released back into the circulation.^{21,22} Glucuronidation is the major metabolic pathway for propofol, and uridine 5'-diphospho-glucuronosyltransferase isoforms are expressed in the kidneys and brain.

Despite the rapid clearance of propofol by metabolism, there is no evidence of impaired elimination in patients with cirrhosis of the liver. Plasma concentrations of propofol at the time of awakening are similar in alcoholic and normal patients.²³ Extrahepatic elimination of propofol occurs during the anhepatic phase of orthotopic liver transplantation. Renal dysfunction does not influence the clearance of propofol despite the observation that nearly three-fourths of propofol metabolites are eliminated in urine in the first 24 hours.²⁴ Patients older than 60 years of age exhibit a decreased rate of plasma clearance of propofol compared with younger adults. The rapid clearance of propofol confirms this drug can be administered as a continuous infusion during surgery without an excessive cumulative effect. Propofol readily crosses the placenta but is rapidly cleared from the neonatal circulation.²⁵ The effect of instituting cardiopulmonary bypass on the plasma propofol concentration is unpredictable, with some studies reporting a decrease, whereas other observations fail to document any change.²⁶

Clinical Uses

Propofol has become the induction drug of choice for many forms of anesthesia, especially when rapid awakening is considered desirable.³ Continuous IV infusion of propofol, with or without other anesthetic drugs, has become a commonly used method for producing IV sedation or as part of a balanced or total IV anesthetic.^{1,3} Administration of propofol as a continuous infusion may be used for sedation of patients in the

ICU.² In this regard, a 2% solution may be useful to decrease the volume of lipid emulsion administered with long-term sedation. A computer-controlled infusion pump is available to allow the clinician to select the propofol target concentration and calculates the infusion rates that are necessary to achieve this target concentration based on the pharmacokinetics of propofol.²⁷ Sadly, introduction of such target-controlled infusion pumps has been met with significant concerns by the U.S. Food and Drug Administration (FDA) over interpatient variability in actual plasma drug concentrations, and they remain unavailable for clinical use in the United States.²⁸

Induction of Anesthesia

The induction dose of propofol in healthy adults is 1.5 to 2.5 mg/kg IV, with blood levels of 2 to 6 µg/mL producing unconsciousness depending on associated medications and the patient's age. As with barbiturates, children require higher induction doses of propofol on a milligram per kilogram basis, presumably reflecting a larger central distribution volume and higher clearance rate. Elderly patients require a lower induction dose (25%-50% decrease) as a result of a smaller central distribution volume and decreased clearance rate and increased pharmacodynamic activity.³ Awakening typically occurs at plasma propofol concentrations of 1.0 to 1.5 µg/mL. Awakening without residual CNS effects that is characteristic of propofol is the principal reason this drug has replaced thiopental for induction of anesthesia in many clinical situations. Thiopental is not currently available for use in the United States.

Intravenous Sedation

The short context-sensitive half-time of propofol, combined with the short effect-site equilibration time, make this a readily titratable drug for production of IV sedation.¹ The prompt recovery without residual sedation and low incidence of nausea and vomiting make propofol particularly well suited to ambulatory conscious sedation techniques. The typical conscious sedation dose of 25 to 100 µg/kg/minute IV produces minimal analgesic and variable amnestic effects.³ In selected patients, midazolam or an opioid may be added to propofol for continuous IV sedation. A sense of well-being may accompany recovery from conscious sedation with propofol. A conventional patient-controlled analgesia delivery system set to deliver 0.7 mg/kg doses of propofol with a 3-minute lockout period has been used as an alternative to continuous IV sedation techniques. Propofol has emerged as the agent of choice for sedation for brief gastrointestinal endoscopy procedures. So reliable are the pharmacologic properties of propofol that extensive design and testing have gone into creation of a computer-assisted personalized sedation for upper endoscopy and colonoscopy, called *SEDASYS*. A comparative, multicenter randomized study concluded that this system could provide endoscopist/nurse teams a safe and effective means to administer propofol to effect minimal to moderate sedation during routine colonoscopy and esophagogastroduodenoscopy without the need for a trained anesthesia provider.²⁹ The *SEDASYS* system received approval from the FDA in 2014 but was withdrawn by the manufacturer in mid-2016 after limited uptake of the device in clinical practice.

Propofol has been administered as a sedative during mechanical ventilation in the ICU in a variety of patient populations including postoperative patients (cardiac surgery, neurosurgery) and patients with head injury.² Propofol also provides control of stress responses and has anticonvulsant and amnestic properties. After cardiac surgery, propofol sedation appears to modulate postoperative hemodynamic responses by decreasing the incidence and severity of tachycardia and hypertension.³⁰ Increasing metabolic acidosis, lipemic plasma, bradycardia, and progressive myocardial failure has been described, particularly in children who were sedated with propofol during management of acute respiratory failure in the ICU.³¹

Maintenance of Anesthesia

The typical dose of propofol for maintenance of anesthesia is 100 to 300 µg/kg/minute IV, often in combination with a short-acting opioid.³ General anesthesia that includes propofol is typically associated with minimal postoperative nausea and vomiting, and awakening is prompt, with minimal residual sedative effects.

Nonhypnotic Therapeutic Applications

In addition to its clinical application as an IV induction drug, propofol has been shown to have beneficial effects that were not anticipated when the drug was initially introduced in 1989.³²

Antiemetic Effects

The incidence of postoperative nausea and vomiting is decreased when propofol is administered, regardless of the anesthetic technique.³² Subhypnotic doses of propofol (10-15 mg IV) may be used in the postanesthesia care unit to treat nausea and vomiting, particularly if it is not of vagal origin. In the postoperative period, the advantage of propofol is its rapid onset of action and the absence of serious side effects. Propofol is generally efficacious in treating postoperative nausea and vomiting at plasma concentrations that do not produce significant sedation. Simulations indicate that antiemetic plasma concentrations of propofol are achieved by a single IV dose of 10 mg followed by 10 µg/kg/minute.³³ Propofol in subhypnotic doses is effective against chemotherapy-induced nausea and vomiting. When administered to induce and maintain anesthesia, it is more effective than ondansetron in preventing postoperative nausea and vomiting.³⁴

Propofol has a profile of CNS depression that differs from other anesthetic drugs. In contrast to thiopental, for example, propofol uniformly depresses CNS structures, including subcortical centers. Most drugs of known antiemetic efficacy exert this effect via subcortical structures, and it is possible that propofol modulates subcortical pathways to inhibit nausea and vomiting or produces a direct depressant effect on the vomiting center. Nevertheless, the mechanisms mediating the antiemetic effects of propofol remain unknown. An antiemetic effect of propofol based on inhibition of dopaminergic activity is unlikely given that subhypnotic doses of propofol fail to increase plasma prolactin concentrations. A rapid and distinct increase in plasma prolactin concentrations is characteristic of drugs that block the dopaminergic system.³⁵ Subhypnotic doses of propofol that are effective as an antiemetic do not inhibit gastric emptying and propofol is not considered a prokinetic drug.³⁶

Antipruritic Effects

Propofol, 10 mg IV, is effective in the treatment of pruritus associated with neuraxial opioids or cholestasis.³⁷ The mechanism of the antipruritic effect may be related to the drug's ability to depress spinal cord activity. In this regard, there is evidence that intrathecal opioids produce pruritus by excitation of neurons within the spinal cord.

Anticonvulsant Activity

Propofol possesses antiepileptic properties, presumably reflecting GABA-mediated presynaptic and postsynaptic inhibition of chloride ion channels. In this regard, propofol in doses of greater than 1 mg/kg IV decreases seizure duration 35% to 45% in patients undergoing electroconvulsive therapy.³⁸

Attenuation of Bronchoconstriction

Compared with thiopental, propofol decreases the prevalence of wheezing after induction of anesthesia and tracheal intubation in healthy and asthmatic patients ([Figure 5.2](#)).³⁹ However, a newer formulation of propofol uses metabisulfite as a preservative. Metabisulfite may cause bronchoconstriction in asthmatic patients. In an animal model, propofol without metabisulfite attenuated vagal nerve stimulation-induced bronchoconstriction, whereas propofol with metabisulfite did not attenuate vagally or methacholine-induced bronchoconstriction and metabisulfite alone caused increases in airway responsiveness.⁴⁰ Following tracheal intubation, in patients with a history of smoking, airway resistance was increased more following the administration of propofol containing metabisulfite than ethylenediaminetetraacetic acid.⁴¹ Therefore, the preservative used for propofol can have effects on its ability to attenuate bronchoconstriction. Nevertheless, propofol-induced bronchoconstriction has been described in patients with allergy histories. The formulation of propofol administered to these patients was Diprivan-containing soybean oil, glycerin, yolk lecithin, and sodium edetate.⁴²

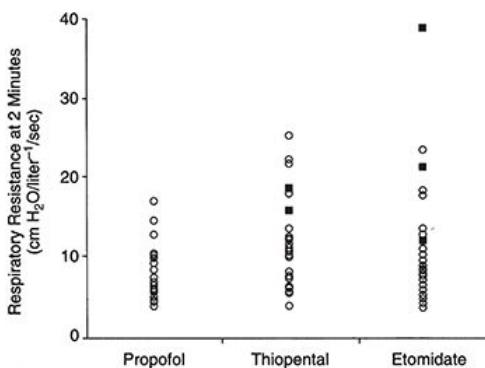


FIGURE 5.2 Respiratory resistance after tracheal intubation is less after induction of anesthesia with propofol than after induction of anesthesia with thiopental or etomidate. The solid squares represent four patients in whom audible wheezing was present. *Reprinted with permission from Eames WO, Rooke GA, Wu RS, et al. Comparison of the effects of etomidate, propofol, and thiopental on respiratory resistance after tracheal intubation. Anesthesiology. 1996;84(6):1307-1311. Copyright © 1996 American Society of Anesthesiologists, Inc.*

Interaction With Opioids

In clinical practice, there is an interaction between propofol and opioid analgesics. These interactions occur both at pharmacokinetic and pharmacodynamic levels. For example, the alfentanil and propofol have an effect on each other's plasma concentrations through changes in elimination and distribution clearance⁴³; coadministration of propofol increases remifentanil concentrations through both a decrease in the central V_d and distributional clearance of remifentanil by 40% and elimination clearance by 15%.⁴⁴ Coadministration of propofol and any of the phenylpiperidines (fentanyl and its congeners) show a synergistic pharmacodynamic interaction. In general, the higher the opioid dose used, the lower the propofol dose required to assure adequate anesthesia.⁴⁴ In the presence of short-acting opioids, it is generally wise to use low-dose propofol infusion regimens. In contrast, in the presence of a longer acting opioids like fentanyl, a high propofol dose/low fentanyl dose anesthetic may lead to a stable anesthetic with a more rapid recovery, postoperatively.

Effects on Organ Systems

Central Nervous System

Propofol decreases cerebral metabolic rate for oxygen ($CMRO_2$), cerebral blood flow, and intracranial pressure (ICP).^{45,46} Administration of propofol to produce sedation in patients with intracranial space-occupying lesions does not increase ICP.⁴⁷ However, large-dose propofol may decrease systemic blood pressure sufficiently to also decrease cerebral perfusion pressure. Cerebrovascular autoregulation in response to changes in systemic blood pressure and reactivity of the cerebral blood flow to changes in $Paco_2$ are not affected by propofol. Cerebral blood flow velocity changes in parallel with changes in $Paco_2$ in the presence of propofol and midazolam (Figure 5.3).⁴⁸ Propofol produces cortical electroencephalographic (EEG) changes that are similar to those of thiopental, including the ability of high doses to produce burst suppression.⁴⁹ Cortical somatosensory evoked potentials as used for monitoring spinal cord function are not significantly modified in the presence of propofol alone but the addition of nitrous oxide or a volatile anesthetic results in decreased amplitude.⁵⁰ Propofol does not interfere with the adequacy of electrocorticographic recordings during awake craniotomy performed for the management of refractory epilepsy, provided administration is discontinued at least 15 minutes before recording.⁵¹ At equal levels of sedation, propofol produces the same degree of memory impairment as midazolam, whereas thiopental has less memory effect and fentanyl has none.⁵²

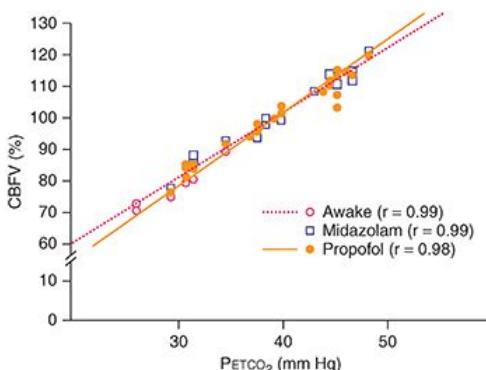


FIGURE 5.3 Changes in the end-tidal PCO_2 (PETCO_2) produce corresponding changes in the cerebral blood flow velocity (CBFV) during infusion of propofol or midazolam. *Reprinted with permission from Streb S, Kaufmann M, Guardiola PM, et al. Cerebral vasomotor responsiveness to carbon dioxide is preserved during propofol and midazolam anesthesia in humans. Anesth Analg. 1994;78(5):884-888. Copyright © 1994 International Anesthesia Research Society.*

Development of tolerance to drugs that depress the CNS is a common finding, occurring with repeated exposure to opioids, sedative-hypnotic drugs, ketamine, and nitrous oxide. However, tolerance to propofol does not develop in children undergoing repeated exposure to the drug during radiation therapy.⁵³

Cardiovascular System

Propofol produces decreases in systemic blood pressure, which are greater than those evoked by comparable doses of thiopental (Figure 5.4).⁵⁴ These decreases in blood pressure are often accompanied by corresponding changes in cardiac output and systemic vascular resistance. The relaxation of vascular smooth muscle produced by propofol is primarily due to inhibition of sympathetic vasoconstrictor nerve activity.⁵⁵ A negative inotropic effect of propofol may result from a decrease in intracellular calcium availability secondary to inhibition of transsarcolemmal calcium influx. Stimulation produced by direct laryngoscopy and intubation of the trachea reverses the blood pressure effects of propofol. Propofol also effectively blunts the hypertensive response to placement of a laryngeal mask airway. The impact of propofol on desflurane-mediated sympathetic nervous system activation is unclear. In one report, propofol 2 mg/kg IV blunted the increase in epinephrine concentration, which accompanied a sudden increase in the delivered desflurane concentration but did not attenuate the transient cardiovascular response.⁵⁶ Conversely, in another report, induction of anesthesia with propofol, but not etomidate, blunted the sympathetic nervous system activation and systemic hypertension associated with the introduction of rapidly increasing inhaled concentrations of desflurane.⁵⁷ The blood pressure effects of propofol may be exaggerated in hypovolemic patients, elderly patients, and patients with compromised left ventricular function. Adequate hydration before rapid IV administration of propofol is recommended to minimize the blood pressure reduction.

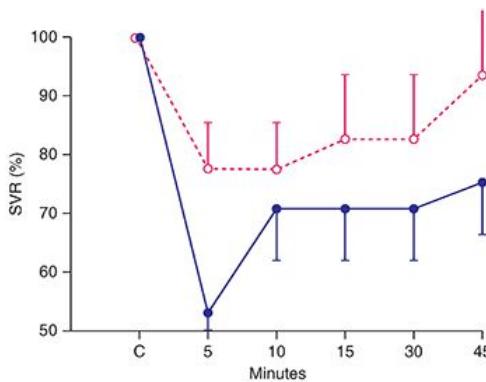


FIGURE 5.4 Comparative changes (expressed in % changes [mean \pm SD]) from control values (C) in systemic vascular resistance (SVR) in the 45 minutes after the administration of thiopental, 5 mg/kg IV (open circles), or propofol, 2.5 mg/kg IV (solid circles). *Reprinted with permission from Rouby JJ, Andreev A, Léger P, et al. Peripheral vascular effects of thiopental and propofol in humans with artificial hearts. Anesthesiology. 1991;75(1):32-42. Copyright © 1991 American Society of Anesthesiologists, Inc.*

Addition of nitrous oxide does not alter the cardiovascular effects of propofol. The pressor response to ephedrine is augmented by propofol ([Figure 5.5](#)).⁵⁸

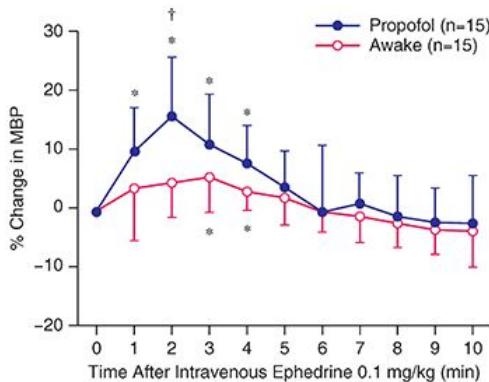


FIGURE 5.5 Mean blood pressure (MBP) increased more following administration of ephedrine (0.1 mg/kg intravenously) to patients during propofol anesthesia than when awake. *Reprinted with permission from Kanaya N, Satoh H, Seki S, et al. Propofol anesthesia enhances the pressor response to intravenous ephedrine. Anesth Analg. 2002;94(5):1207-1211. Copyright © 2002 International Anesthesia Research Society.*

Despite decreases in systemic blood pressure, heart rate typically remains unchanged. Baroreceptor reflex control of heart rate may be depressed by propofol.⁵⁹ However, bradycardia and asystole have been observed after induction of anesthesia with propofol, resulting in the occasional recommendation that anticholinergic drugs be administered when vagal stimulation is likely to occur in association with administration of propofol (see the “[Bradycardia-Related Death](#)” section). Propofol may decrease sympathetic nervous system activity to a greater extent than parasympathetic nervous system activity, resulting in a predominance of parasympathetic activity.¹ Propofol does not alter sinoatrial or atrioventricular node function in normal patients or in patients with Wolff-Parkinson-White syndrome, thus making it an acceptable drug to administer during ablative procedures.^{60,61} Nevertheless, there is a case report of a patient with Wolff-Parkinson-White syndrome in whom delta waves on the electrocardiogram disappeared during infusion of propofol.⁶² Unlike sevoflurane, propofol does not prolong the QTc interval on the electrocardiogram.⁶³

Bradycardia-Related Death

Profound bradycardia and asystole after administration of propofol have been described in healthy adult patients, despite prophylactic anticholinergics.⁶⁴⁻⁶⁷ The risk of bradycardia-related death during propofol anesthesia has been estimated to be 1.4 in 100,000. Propofol anesthesia, compared with other anesthetics, increases the incidence of the oculocardiac reflex in pediatric strabismus surgery, despite prior administration of anticholinergics.⁶⁸ Heart rate responses to IV administration of atropine are attenuated in patients receiving propofol compared with awake patients ([Figure 5.6](#)).⁶⁹ This decreased responsiveness to atropine cannot be effectively overcome by larger doses of atropine suggesting that propofol may induce suppression of sympathetic nervous system activity. Treatment of propofol-induced bradycardia may require treatment with a direct β -agonist such as isoproterenol.

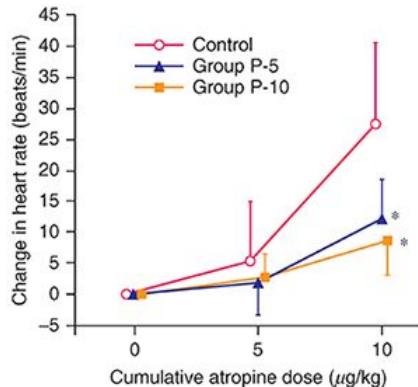


FIGURE 5.6 Heart rate responses to cumulative intravenous (IV) atropine doses in patients receiving no propofol, patients receiving 5 mg/kg/hour IV (group P-5), and patients receiving 10 mg/kg/hour IV (group P-10). Mean \pm standard deviation. * $P < .05$ compared with the control group. Reprinted with permission from Horiguchi T, Nishikawa T. Heart rate response to intravenous atropine during propofol anesthesia. Anesth Analg. 2002;95(2):389-392. Copyright © 2002 International Anesthesia Research Society.

Lungs

Propofol produces dose-dependent depression of ventilation, with apnea occurring in 25% to 35% of patients after induction of anesthesia with propofol.⁷⁰ Opioids administered with the preoperative medication enhances ventilatory depressant. Painful surgical stimulation is likely to counteract the ventilatory depressant effects of propofol. A maintenance infusion of propofol decreases tidal volume and frequency of breathing. The ventilatory response to arterial hypoxemia are also decreased by propofol due to an effect at the central chemoreceptors.⁷¹ Likewise, propofol at sedative doses significantly decreases the slope and causes a downward shift of the ventilatory response curve to hypoxia.⁷² Hypoxic pulmonary vasoconstriction seems to remain intact in patients receiving propofol.

Hepatic and Renal Function

Propofol does not normally affect hepatic or renal function as reflected by measurements of liver transaminase enzymes or creatinine concentrations. Prolonged infusions of propofol have been associated with hepatocellular injury accompanied by lactic acidosis, bradycardias, and rhabdomyolysis as part of the propofol infusion syndrome described in the following text. In rare instances, presumed propofol-induced hepatocellular injury following uneventful anesthesia and surgery has been described.⁷³ Prolonged infusions of propofol may also result in excretion of green urine, reflecting the presence of phenols in the urine. This discoloration does not alter renal function. Urinary uric acid excretion is increased after administration of propofol and may manifest as cloudy urine when the uric acid crystallizes in the urine under conditions of low pH and temperature.²⁴ This cloudy urine is not considered to be detrimental or indicative of adverse renal effects of propofol.

Intraocular Pressure

Laparoscopic surgery is associated with increased intraocular pressure, and some consider laparoscopic surgery with the head-down position a risk in the presence of preexisting ocular hypertension. In this regard, propofol is associated with significant decreases in intraocular pressure that occur immediately after induction of anesthesia and are sustained during tracheal intubation.¹ Total IV anesthesia with propofol for laparoscopic surgery was associated with lower intraocular pressures than in patients undergoing similar surgery with isoflurane anesthesia (Figure 5.7).⁷⁴

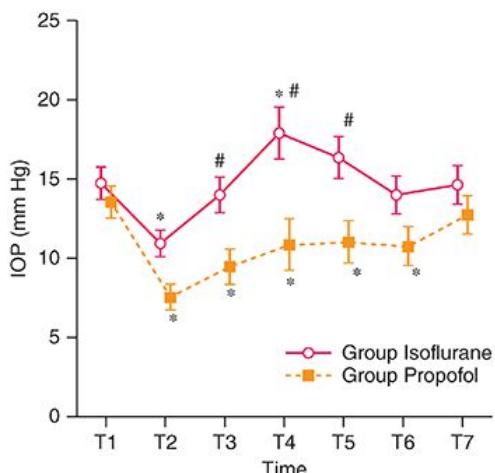


FIGURE 5.7 Changes in intraocular pressure (IOP) in patients receiving isoflurane or propofol. Measurements were made before induction of anesthesia (T1), after induction of anesthesia (T2), after pneumoperitoneum (T3), after head-down position (T4), after return to neutral supine position (T5), after evacuation of pneumoperitoneum (T6), and in the postanesthesia care unit (T7). Abbreviations: *, significant difference compared with T1; #, significant difference between the isoflurane and propofol groups. Reprinted with permission from Mowafi HA, Al-Ghamdi A, Rushood A. Intraocular pressure changes during laparoscopy in patients anesthetized with propofol total intravenous anesthesia versus isoflurane inhaled anesthesia. Anesth Analg. 2003;97(2):471-474. Copyright © 2003 International Anesthesia Research Society.

Coagulation

Propofol does not alter tests of coagulation or platelet function. This is reassuring because the emulsion in which propofol is dispensed resembles intralipid, which has been associated with alterations in blood coagulation. However, propofol inhibits platelet aggregation that is induced by proinflammatory lipid mediators including thromboxane A₂ and platelet-activating factor.⁷⁵

Other Side Effects

Side effects of propofol may reflect the parent drug or actions attributed to the oil-in-water emulsion formulation. For example, some of the side effects of propofol (bradycardia, risk of infection, pain on injection, hypertriglyceridemia with prolonged administration, potential for pulmonary embolism) are believed to be due in large part to the lipid emulsion formulation.^{8,9}

Allergic Reactions

Allergenic components of propofol include the phenyl nucleus and diisopropyl side chain.⁷⁶ Patients who develop evidence of anaphylaxis on first exposure to propofol may have been previously sensitized to the diisopropyl radical, which is present in many dermatologic preparations. Likewise, the phenol nucleus is common to many drugs. Indeed, anaphylaxis to propofol during the first exposure to this drug has been observed, especially in patients with a history of other drug allergies, often to neuromuscular blocking drugs.⁷⁷ Propofol-induced bronchoconstriction has been described in patients with allergy histories.⁴² The formulation of propofol administered to these patients was Diprivan-containing soybean oil, glycerin, yolk lecithin, and sodium edetate.

Lactic Acidosis

Lactic acidosis (“propofol infusion syndrome”) has been described in pediatric and adult patients receiving prolonged high-dose infusions of propofol (>75 µg/kg/minute) for longer than 24 hours.^{78,79} Severe, refractory, and fatal bradycardia in children in the ICU has been observed with long-term propofol

sedation.^{80,81} Even short-term infusions of propofol (Diprivan) for surgical anesthesia have been associated with development of metabolic acidosis.^{82,83} Unexpected tachycardia occurring during propofol anesthesia should prompt laboratory evaluation for metabolic (lactic) acidosis. Measurement of arterial blood gases and serum lactate concentrations is recommended. Documentation of an increased ion gap is useful, followed by prompt discontinuation of propofol administration.⁸⁴ If the results of laboratory studies are delayed, propofol should be discontinued while awaiting results. Metabolic acidosis in its early stages is reversible with discontinuation of propofol administration, although cardiogenic shock requiring assistance with extracorporeal membrane oxygenation has been described in a patient receiving a prolonged propofol infusion (Diprivan) for a craniotomy.⁸⁵

The mechanism for sporadic propofol-induced metabolic acidosis is unclear but may reflect poisoning (cytotoxic hypoxia) of the electron transport chain and impaired oxidation of long chain fatty acids by propofol or a propofol metabolite in uniquely susceptible patients.⁸⁶ Indeed, this propofol infusion syndrome mimics the mitochondrial myopathies, in which there are specific defects in the mitochondrial respiratory chain associated with specific mitochondrial DNA abnormalities, resulting in abnormal lipid metabolism in cardiac and skeletal muscles. These individuals, who are probably genetically susceptible, remain asymptomatic until a triggering event (sepsis, malnutrition) intervenes. The differential diagnosis when propofol-induced lactic acidosis is suspected includes hyperchloremic metabolic acidosis associated with large volume infusions of 0.9% saline and metabolic acidosis associated with excessive generation of organic acids, such as lactate and ketones (diabetic acidosis, release of a tourniquet). Measurement of the anion gap and individual measurements of anions and organic acids will differentiate hyperchloremic metabolic acidosis from lactic acidosis.

Proconvulsant Activity

The majority of reported propofol-induced “seizures” during induction of anesthesia or emergence from anesthesia reflect spontaneous excitatory movements of subcortical origin.³² These responses are not thought to be due to cortical epileptic activity. Prolonged myoclonus associated with meningismus has been associated with propofol administration.⁸⁷ The incidence of excitatory movements and associated electrocardiogram changes are low after the administration of propofol.⁸⁸ Propofol resembles thiopental in that it does not produce seizure activity on the EEG when administered to patients with epilepsy, including those undergoing cortical resection.⁴⁹ There appears to be no reason to avoid propofol for sedation, induction, and maintenance of anesthesia in patients with known seizures.¹²

Abuse Potential

Intense dreaming activity, amorous behavior, and hallucinations have been reported during recovery from low-dose infusions of propofol.³² Addiction to virtually all opioids and hypnotics, including propofol, has been described.^{89,90} The death of music pop star Michael Jackson in 2009 from an overdose of propofol he was receiving as a sleep aid has brought the dangers of propofol misuse to public attention.⁹¹

Bacterial Growth

Propofol strongly supports the growth of *Escherichia coli* and *Pseudomonas aeruginosa*, whereas the solvent (Intralipid) appears to be bactericidal for these same organisms and bacteriostatic for *Candida albicans*.⁹² Clusters of postoperative surgical infections manifesting as temperature elevations have been attributed to extrinsic contamination of propofol.^{93,94} For this reason, it is recommended that (1) an aseptic technique be used in handling propofol as reflected by disinfecting the ampule neck surface or vial rubber stopper with 70% isopropyl alcohol, (2) the contents of the ampule containing propofol should be withdrawn into a sterile syringe immediately after opening and administered promptly, and (3) the contents of an opened ampule must be discarded if they are not used within 6 hours. In the ICU, the tubing and any unused portion of propofol must be discarded after 12 hours. Despite these concerns, there is evidence that when propofol is aseptically drawn into an uncapped syringe, it will remain sterile at room temperature for several days.⁹⁵ Given the cost

of propofol, some have questioned the logic of discarding unused drug at the end of an anesthetic or 6 hours, whichever occurs sooner.³

Antioxidant Properties

Propofol has potent antioxidant properties that resemble those of the endogenous antioxidant vitamin E.^{96,97} Like vitamin E, propofol contains a phenolic hydroxyl group that scavenges free radicals and inhibits lipid peroxidation. A neuroprotective effect of propofol may be at least partially related to the antioxidant potential of propofol's phenol ring structure. For example, propofol reacts with lipid peroxy radicals and thus inhibits lipid peroxidation by forming relatively stable propofol phenoxy radicals. In addition, propofol also scavenges peroxy nitrite, which is one of the most potent reactive metabolites for the initiation of lipid peroxidation. Because peroxy nitrite is a potent bactericidal agent, it is likely that the peroxy nitrite-scavenging activity of propofol contributes to this anesthetic's known ability to suppress phagocytosis.⁹⁸ Conversely, propofol might be beneficial in disease states, such as acute lung injury, in which peroxy nitrite formation is thought to play an important role.⁹⁹

Reintroduction of molecular oxygen into previously ischemic tissues (removal of an aortic cross-clamp) can further damage partially injured cells (reperfusion injury). Oxygen leads to the formation of free oxygen radicals, which react with polyunsaturated fatty acids of cell membranes resulting in disruption of cell membranes. Myocardial cell injury can cause postischemic dysfunction, myocardial stunning, and reperfusion cardiac dysrhythmias. Propofol strongly attenuates lipid peroxidation during coronary artery bypass graft surgery.¹⁰⁰

Pain on Injection

Pain on injection is the most commonly reported adverse event associated with propofol administration to awake patients. This unpleasant side effect of propofol occurs in less than 10% of patients when the drug is injected into a large vein rather than a dorsum vein on the hand. Preceding the propofol with (using the same injection site as for propofol) 1% lidocaine or by prior administration of a potent short-acting opioid decreases the incidence of discomfort experienced by the patient. The incidence of thrombosis or phlebitis is usually less than 1%. Changing the composition of the carrier fat emulsion for propofol to long and medium chain triglycerides decreases the incidence of pain on injection.¹⁰¹

Accidental intra-arterial injection of propofol has been described as producing severe pain but no vascular compromise.¹⁰² In an animal model, propofol-exposed arteries showed no changes in the vascular smooth muscle, and the endothelium was not damaged.¹⁰³

Airway Protection

Inhaled and injected anesthetic drugs alter pharyngeal function with the associated risk of impaired upper airway protection and pulmonary aspiration. Subhypnotic concentrations of propofol, isoflurane, and sevoflurane decrease pharyngeal contraction force.¹⁰⁴

Miscellaneous Effects

Propofol does not trigger malignant hyperthermia and has been administered to patients with hereditary coproporphyrin without incident.¹⁰⁵⁻¹⁰⁷ Secretion of cortisol is not influenced by propofol, even when administered for prolonged periods in the ICU. Temporary abolition of tremors in patients with Parkinson disease may occur after the administration of propofol.¹⁰⁸ For this reason, propofol may not be ideally suited for patients undergoing stereotactic neurosurgery during which the symptom is required to identify the correct anatomic location.

Etomidate

Etomidate is a carboxylated imidazole-containing compound that is chemically unrelated to any other drug used for the IV induction of anesthesia.¹⁰⁹ The imidazole nucleus renders etomidate, like midazolam, water-soluble at an acidic pH and lipid-soluble at physiologic pH.

Commercial Preparation

The original formulation of etomidate included 35% propylene glycol (pH 6.9) contributing to a high incidence of pain during IV injection and occasional venous irritation. This has been changed to a fat emulsion, which has virtually abolished pain on injection and venous irritation, whereas the incidence of myoclonus remains unchanged. An oral formulation of etomidate for transmucosal delivery has been shown to produce dose-dependent sedation.¹¹⁰ Administration through the oral mucosa results in systemic absorption while bypassing hepatic metabolism. As a result, higher blood concentrations are achieved more rapidly compared with drug that is administered by mouth.

Mechanism of Action

Etomidate is unique among injected and inhaled anesthetics in being administered as a single isomer.¹⁰⁹ The anesthetic effect of etomidate resides predominantly in the R(+) isomer, which is approximately 5 times as potent as the S(−) isomer. In contrast to barbiturates, etomidate appears to be relatively selective as a modulator of GABA_A receptors. Stereoselectivity of etomidate supports the concept that GABA_A receptors are the site of action of etomidate. Etomidate exerts its effects on GABA_A receptors by binding directly to a specific site or sites on the protein and enhancing the affinity of the inhibitory neurotransmitter (GABA) for these receptors.¹⁰⁹ Antagonism of steroid-induced psychosis by etomidate is consistent with enhancement of GABA receptor function by this anesthetic drug.¹¹¹ Etomidate is not known to modulate other ligand-gated ion channels in the brain at clinically relevant concentrations.

Pharmacokinetics

The V_d of etomidate is large, suggesting considerable tissue uptake (see **Table 5.1**). Distribution of etomidate throughout body water is favored by its moderate lipid solubility and existence as a weak base (pK 4.2, pH 8.2, 99% unionized at physiologic pH). Etomidate penetrates the brain rapidly, reaching peak levels within 1 minute after IV injection. About 76% of etomidate is bound to albumin independently of the plasma concentration of the drug. Decreases in plasma albumin concentrations result in dramatic increases in the unbound pharmacologically active fraction of etomidate in the plasma. Prompt awakening after a single dose of etomidate principally reflects the redistribution of the drug from brain to inactive tissue sites. Rapid metabolism is also likely to contribute to prompt recovery.

Metabolism

Etomidate is rapidly metabolized by hydrolysis of the ethyl ester side chain to its carboxylic acid ester, resulting in a water-soluble, pharmacologically inactive compound. Hepatic microsomal enzymes and plasma esterases are responsible for this hydrolysis. Hydrolysis is nearly complete, as evidenced by recovery of less than 3% of an administered dose of etomidate as unchanged drug in urine. About 85% of a single IV dose of etomidate can be accounted for as the carboxylic acid ester metabolite in urine, whereas another 10% to 13% is present as this metabolite in the bile. Overall, the clearance of etomidate is somewhat slower than that for propofol (18-25 mL/kg/minute vs 20-30 mL/kg/minute, respectively). The V_d for etomidate is about half that of propofol (2.5-4.5 L/kg vs 2-10 L/kg, respectively).¹¹²⁻¹¹⁴ Slower clearance will delay elimination, while a small V_d will result in more rapid elimination. In the case of etomidate, the effect of volume dominates, and etomidate has a shorter terminal elimination half-life (3-5 hours) than propofol (4-7 hours). Likewise, the context-sensitive half-time (the time for the plasma level of the drug to drop 50% after cessation of infusion) of etomidate is less likely to be increased by continuous infusion as compared with propofol.

Cardiopulmonary Bypass

Institution of hypothermic cardiopulmonary bypass causes an initial decrease of about 34% in the plasma etomidate concentration that then returns to within 11% of the pre-bypass value only to be followed by a further decrease with rewarming.²⁶ The return of the plasma concentration toward pre-bypass levels is attributed to decreased metabolism, and the subsequent decrease on rewarming is attributed to increased

metabolism. In addition, hepatic blood flow changes during cardiopulmonary bypass may alter metabolism, as etomidate is a high-hepatic extraction drug.

Clinical Uses

Etomidate may be viewed as an alternative to propofol or barbiturates for the IV induction of anesthesia, especially in the presence of an unstable cardiovascular system. After a standard induction dose of 0.2 to 0.4 mg/kg IV, the onset of unconsciousness occurs within one arm-to-brain circulation time. Involuntary myoclonic movements are common during the induction period as a result of alteration in the balance of inhibitory and excitatory influences on the thalamocortical tract. The frequency of this myoclonic-like activity can be attenuated by prior administration of an opioid. Awakening after a single IV dose of etomidate is more rapid than after barbiturates and similar to that of propofol. This has been tested in numerous settings, including induction of anesthesia for electroconvulsive therapy³⁶ and for cardioversion,¹¹⁵ where awakening occurs within 5 to 15 minutes after doses of etomidate ranging from 0.1 to 0.3 mg/kg and propofol ranging from 0.75 to 1.5 mg/kg,¹¹⁵ and there is little or no evidence of a hangover or cumulative drug effect. Full recovery of psychomotor function after administration of etomidate is somewhat slower than following use of propofol. The duration of action is prolonged by increasing the dose of etomidate or administering the drug as a continuous infusion. As with barbiturates and propofol, analgesia is not produced by etomidate. For this reason, administration of an opioid before induction of anesthesia with etomidate may be useful to blunt the hemodynamic responses evoked by direct laryngoscopy and tracheal intubation. Etomidate, 0.15 to 0.3 mg/kg IV, has minimal effects on the duration of electrically induced seizures and thus may serve as an alternative to drugs that decrease the duration of seizures (propofol, thiopental) in patients undergoing electroconvulsive therapy.³⁸

The principal limiting factor in the clinical use of etomidate for induction of anesthesia is the ability of this drug to transiently depress adrenocortical function (see the “[Adrenocortical Suppression](#)” section). It is widely viewed that postoperative nausea and vomiting is increased in patients receiving etomidate for induction of anesthesia.¹¹⁶ Nevertheless, comparison of etomidate with propofol did not document an increased incidence of nausea and vomiting in the first 24 hours after surgery in patients receiving etomidate.¹¹⁷

Side Effects

Central Nervous System

Etomidate is a potent direct cerebral vasoconstrictor that decreases cerebral blood flow and CMRO₂ 35% to 45%.¹¹⁸ As a result, previously increased ICP is lowered by etomidate. These effects of etomidate are similar to those changes produced by comparable doses of propofol. Suppression of adrenocortical function limits the clinical usefulness for long-term treatment of intracranial hypertension (see the “[Adrenocortical Suppression](#)” section).

Etomidate produces a pattern on the EEG that is similar to thiopental and propofol. However, the frequency of excitatory spikes on the EEG is greater with etomidate than with propofol, thiopental, and methohexital, suggesting caution in administration of etomidate to patients with a history of seizures.⁸⁸ Like methohexital, etomidate may activate seizure foci, manifesting as fast activity on the EEG.¹¹⁹ For this reason, etomidate should also be used with caution in patients with focal epilepsy. Conversely, this characteristic has been observed to facilitate localization of seizure foci in patients undergoing cortical resection of epileptogenic tissue. Etomidate also possesses anticonvulsant properties and has been used to terminate status epilepticus. Etomidate has been observed to augment the amplitude of somatosensory evoked potentials, making monitoring of these responses more reliable.¹²⁰

Cardiovascular System

Cardiovascular stability is characteristic of induction of anesthesia with 0.3 mg/kg IV of etomidate. After this dose of etomidate, there are minimal changes in heart rate, stroke volume, or cardiac output, whereas mean arterial blood pressure may decrease up to 15% because of decreases in systemic vascular resistance. The

decrease in systemic blood pressure in parallel with changes in systemic vascular resistance suggests that administration of etomidate to acutely hypovolemic patients could result in sudden hypotension. When an induction dose of etomidate is 0.45 mg/kg IV, significant decreases in systemic blood pressure and cardiac output may occur.¹²¹ During induction of patients undergoing elective cardiac surgery, propofol caused a significantly greater decline in mean arterial pressure (MAP) than etomidate, while changes in other hemodynamic parameters were not significantly changed.¹²²

Effects of etomidate on myocardial contractility are important to consider, as this drug has been proposed for induction of anesthesia in patients with little or no cardiac reserve. It is difficult to document anesthetic-induced negative inotropic effects *in vivo* because of concurrent changes in preload, afterload, sympathetic nervous system activity, and baroreceptor reflex activity. Therefore, direct effects of anesthetics on intrinsic myocardial contractility may be more accurately assessed *in vitro*. Etomidate causes dose-dependent decreases in developed tension in isolated cardiac muscle obtained from patients undergoing coronary artery bypass graft operations or cardiac transplantation (Figure 5.8).¹²³ This depression was reversible with β -adrenergic stimulation. Nevertheless, concentrations required to produce these negative inotropic effects are in excess of those achieved with clinical use. Thus, etomidate may differ from most other IV anesthetics in that depressive effects on myocardial contractility are minimal at concentrations needed for the production of anesthesia. Hepatic and renal functions tests are not altered by etomidate. Intraocular pressure is decreased by etomidate to a similar degree as by propofol. Etomidate does not result in detrimental effects when accidentally injected into an artery.

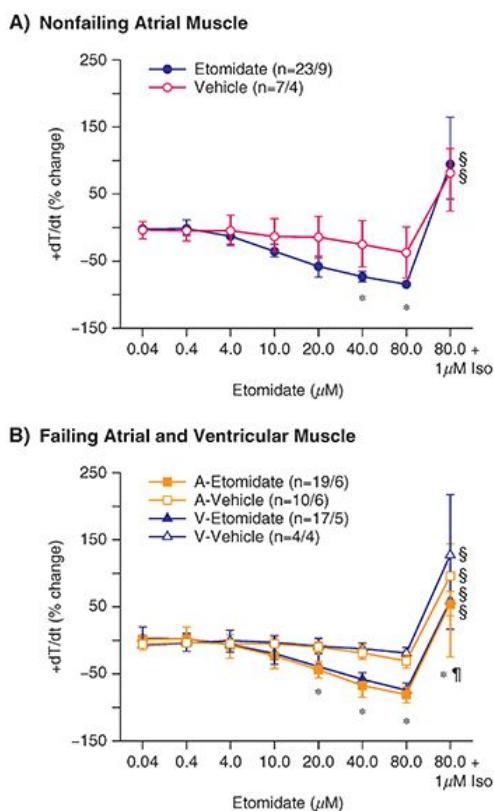


FIGURE 5.8 Effects of etomidate on maximal rate of contraction ($+dT/dt$) in nonfailing atrial muscle (A) and in failing atrial and ventricular muscle (B). Mean \pm standard deviation. * $P < .05$ versus vehicle.

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Ventilation

The depressant effects of etomidate on ventilation seem to be less than those of barbiturates and propofol, although apnea may occasionally accompany a rapid IV injection of the drug.¹²⁴ In the majority of patients, etomidate-induced decreases in tidal volume are offset by compensatory increases in the frequency of breathing. These effects on ventilation are transient, lasting only 3 to 5 minutes. Etomidate may stimulate ventilation independently of the medullary centers that normally respond to carbon dioxide. For this reason, etomidate may be useful when maintenance of spontaneous ventilation is desirable. However, careful analysis of the impact of equipotent doses of etomidate on respiration in comparison to other sedative-hypnotics has not been conducted. A recent Cochrane Database review of 23 trials comparing various anesthetic and sedative agents for cardioversion concluded that there were no discernible differences among agents or combinations of agents using in this common setting.¹²⁵ Depression of ventilation may be exaggerated when etomidate is combined with inhaled anesthetics or opioids during continuous infusion techniques.

Pain on Injection

Pain on injection and venous irritation has been virtually eliminated with use of etomidate in a lipid emulsion vehicle rather than propylene glycol.

Myoclonus

Commonly administered IV anesthetics can cause excitatory effects that may manifest as spontaneous movements, such as myoclonus, dystonia, and tremor. These spontaneous movements, particularly myoclonus, occur in 50% to 80% of patients receiving etomidate in the absence of premedication.⁸⁸ In one report, 87% of patients receiving etomidate developed excitatory effects, of which 69% were myoclonic. Multiple spikes appeared on the EEG of 22% of these patients.⁸⁸ In this same report, the frequency of excitatory effects was 17% after thiopental, 13% after methohexital, and 6% after propofol, and none of the patients treated with other drugs developed myoclonus with spike activity on the EEG.⁸⁸ Inclusion of atropine in the preoperative medication may suppress spike activity on the EEG associated with the administration of etomidate. Prior administration of an opioid (fentanyl, 1-2 µg/kg IV) or a benzodiazepine may decrease the incidence of myoclonus associated with administration of etomidate. Furthermore, the incidence and intensity of myoclonus following the administration of etomidate is dose related and suppressed by pretreatment with small doses of etomidate (0.03-0.075 mg/kg IV) before administration of the induction dose.¹²⁶

The mechanism of etomidate-induced myoclonus appears to be disinhibition of subcortical structures that normally suppress extrapyramidal motor activity. In many patients, excitatory movements are coincident with the early slow phase of the EEG, which corresponds to the beginning of deep anesthesia.⁸⁸ It is possible that myoclonus could occur on awakening if the extrapyramidal system emerged more quickly than the cortex that inhibits it.¹²⁷ Others have not documented seizure-like activity on the EEG in association with etomidate-induced myoclonus.¹²⁶

Adrenocortical Suppression

Etomidate causes adrenocortical suppression by producing a dose-dependent inhibition of the conversion of cholesterol to cortisol (**Figure 5.9**).^{128,129} The specific enzyme inhibited by etomidate appears to be 11-β-hydroxylase as evidenced by the accumulation of 11-deoxycorticosterone.¹³⁰ This enzyme inhibition lasts 4 to 8 hours after an induction dose of etomidate. Conceivably, patients experiencing sepsis or hemorrhage and who might require an intact cortisol response would be at a disadvantage should etomidate be administered.¹³¹ Conversely, suppression of adrenocortical function could be considered desirable from the standpoint of “stress-free” anesthesia. Nevertheless, in at least one report, it was not possible to demonstrate a difference in the plasma concentrations of cortisol, corticosterone, or adrenocorticotropic hormone in patients receiving a single dose of etomidate or thiopental.¹³² In a retrospective study of almost 1,700 trauma patients receiving a single induction dose of etomidate or another induction agent, use of etomidate had no impact on mortality, length of ICU stay, or duration of mechanical ventilation.¹³³ In a retrospective study of more than 3,000 cardiac surgical patients who received etomidate for induction of anesthesia, there was no

evidence to suggest that etomidate exposure was associated with severe hypotension, longer mechanical ventilation hours, longer length of hospital stay, or in-hospital mortality.¹³⁴ In contrast, another large-scale retrospective study demonstrated that anesthetic induction with etomidate, rather than propofol, was associated with increased 30-day mortality and cardiovascular morbidity after noncardiac surgery.¹³⁵ The clinical benefit of minimizing cardiac suppression should be carefully weighed against the potential for worsened long-term outcomes when using propofol in high-risk patients.

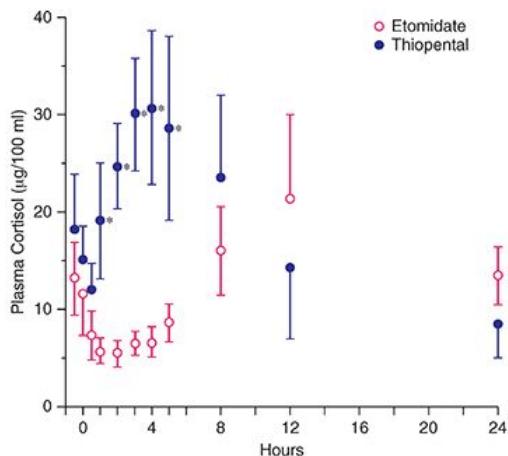


FIGURE 5.9 Etomidate, but not thiopental, is associated with decreases in the plasma concentrations of cortisol. Mean \pm standard deviation. * $P < .05$ compared with thiopental. Reprinted with permission from Fragen RJ, Shanks CA, Molteni A, et al. Effects of etomidate on hormonal responses to surgical stress. *Anesthesiology*. 1984;61(6):652-656. Copyright © 1984 American Society of Anesthesiologists, Inc.

Allergic Reactions

The incidence of allergic reactions following administration of etomidate is very low.¹³⁶ When reactions have occurred, it is difficult to separate the role of etomidate from other concomitantly administered drugs (neuromuscular blocking drugs) that are more likely to evoke histamine release than etomidate.

Benzodiazepines

Benzodiazepines are drugs that exert, in slightly varying degrees, five principal pharmacologic effects: anxiolysis, sedation, anticonvulsant actions, spinal cord-mediated skeletal muscle relaxation, and anterograde amnesia (acquisition or encoding of new information).¹³⁷ The amnestic potency of benzodiazepines is greater than their sedative effects resulting in a longer duration of amnesia than sedation. Stored information (retrograde amnesia) is not altered by benzodiazepines.¹³⁸ Benzodiazepines do not produce adequate skeletal muscle relaxation for surgical procedures nor does their use influence the required dose of neuromuscular blocking drugs. The frequency of anxiety and insomnia in clinical practice combined with the efficacy of benzodiazepines has led to widespread use of these drugs. For example, it is estimated that 4% of the population uses “sleeping pills” sometime during a given year, and 0.4% of the population uses hypnotics for more than a year.¹³⁹ Although benzodiazepines are effective for the treatment of acute insomnia, their use for management of chronic insomnia is decreasing as their impact on cognitive function and mortality have emerged.¹⁴⁰ Compared with barbiturates, benzodiazepines have fewer tendencies to produce tolerance, less potential for abuse, a greater margin of safety, and elicit fewer and less serious drug interactions. Unlike barbiturates, benzodiazepines do not induce hepatic microsomal enzymes. Benzodiazepines are intrinsically far less addicting than opioids, cocaine, amphetamines, or barbiturates.

Midazolam is the most commonly used benzodiazepine in the perioperative period. Furthermore, the context-sensitive half-times for diazepam and lorazepam are prolonged; therefore, only midazolam is likely to be used for prolonged administration when prompt recovery is desired. However, the longer context-

sensitive half-time of lorazepam makes this drug an attractive choice to facilitate sedation of patients in critical care environments. Unlike other drugs administered IV to produce CNS effects, benzodiazepines, as a class of drugs, are unique in the availability of a specific pharmacologic antagonist, *flumazenil*. Structurally, benzodiazepines are similar and share many active metabolites. The duration of action of benzodiazepines is not linked to receptor events but rather is determined by the rate of metabolism and elimination. Importantly, benzodiazepines do not produce enzyme induction.

Mechanism of Action

Benzodiazepines appear to produce all their pharmacologic effects by facilitating the actions of GABA.¹⁴¹ Benzodiazepines do not activate the GABA_A receptors but rather enhance the affinity of the receptors for GABA (Figure 5.10).¹⁴² As a result of increased affinity for GABA, there is a greater probability of chloride channel openings, resulting in increased chloride conductance and hyperpolarization of the postsynaptic cell membrane. The postsynaptic neurons are thus rendered more resistant to excitation. This resistance to excitation is presumed to be the mechanism by which benzodiazepines produce anxiolysis, sedation, anterograde amnesia, alcohol potentiation, and anticonvulsant and skeletal muscle relaxant effects.

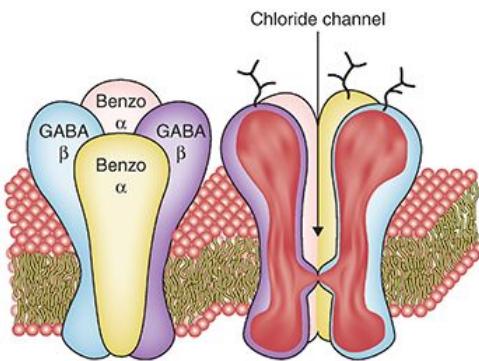


FIGURE 5.10 Model of the γ -aminobutyric acid (GABA) receptor forming a chloride channel. Benzodiazepines (benzo) attach selectively to α subunits and are presumed to facilitate the action of the inhibitory neurotransmitter GABA on α subunits. Reprinted with permission from Möhler H, Richards JG. *The benzodiazepine receptor: a pharmacologic control element of brain function*. Eur J Anaesthesiol Suppl. 1988;2:15-24. Copyright © 1988 European Society of Anaesthesiology.

Benzodiazepines interact with a site located between the α and γ subunits of the GABA_A receptor. The γ subunit is required for benzodiazepine binding. The α_1 - and α_5 -containing GABA_A receptors are important for sedation, whereas anxiolytic activity is due to interaction with α_2 and α_5 subunit-containing receptors.^{143,144} The α_1 -containing GABA_A receptors are the most abundant receptor subtypes accounting for approximately 60% of GABA_A receptors in the brain. The α_2 subunits have more restricted expression, principally in the hippocampus and amygdala. The α_5 -containing GABA_A receptors are principally extrasynaptic and are responsible for modulation of the resting membrane potential. This anatomic distribution of receptors is consistent with the minimal effects of these drugs outside the CNS (minimal circulatory effects). In the future, it may be possible to design benzodiazepines that selectively activate specific GABA_A receptor types to produce anxiolysis without sedation.

The GABA_A receptor is a large macromolecule that contains physically separate binding sites (principally α , β , and γ subunits) not only for GABA and the benzodiazepines but also barbiturates, etomidate, propofol, steroids, and alcohol. Acting on a single receptor at different binding sites, the benzodiazepines, barbiturates, and alcohol can produce synergistic effects to increase GABA_A receptor-mediated inhibition in the CNS. This property explains the pharmacologic synergy of these substances and, likewise, the risks of combined overdose, which can produce life-threatening CNS depression. This synergy is also the basis for pharmacologic cross-tolerance between these different classes of drugs and is consistent

with the clinical use of benzodiazepines as the first-choice drugs for detoxication from alcohol. Conversely, benzodiazepines have a built-in ceiling effect that prevents them from exceeding the physiologic maximum of GABA inhibition. The low toxicity of the benzodiazepines and their corresponding clinical safety is attributed to this limitation of their effect on GABAergic neurotransmission.

Differences in the onset and duration of action among commonly administered benzodiazepines reflect differences in potency (receptor binding affinity), lipid solubility (ability to cross the blood–brain barrier and redistribute to peripheral tissues), and pharmacokinetics (uptake, distribution, metabolism, and elimination). All benzodiazepines are highly lipid soluble and are highly bound to plasma proteins, especially albumin. Hypoalbuminemia owing to hepatic cirrhosis or chronic renal failure may increase the unbound fraction of benzodiazepines, resulting in enhanced clinical effects produced by these drugs. Following oral administration, benzodiazepines are highly absorbed from the gastrointestinal tract, and after IV injection, they rapidly enter the CNS and other highly perfused organs.

Nucleoside Transporter Systems

Benzodiazepines decrease adenosine degradation by inhibiting the nucleoside transporter, which is the principal mechanism whereby the effect of adenosine is terminated through reuptake into cells.¹⁴⁵ Adenosine is an important regulator of cardiac function (reduces cardiac oxygen demand by slowing heart rate and increases oxygen delivery by causing coronary vasodilation), and its physiologic effects convey cardioprotection during myocardial ischemia.

Electroencephalogram

The effects of benzodiazepines on the EEG resemble those of barbiturates in that α activity is decreased and low-voltage rapid β activity is increased. This shift from α to β activity occurs more in the frontal and rolandic areas with benzodiazepines, which, unlike the barbiturates, do not cause posterior spread. In common with barbiturates, however, tolerance to the effects of benzodiazepines on the EEG does not occur. Midazolam, in contrast to barbiturates and propofol, is unable to produce an isoelectric EEG.

Side Effects

Fatigue and drowsiness are the most common side effects in patients treated chronically with benzodiazepines. Sedation that could impair performance usually subsides within 2 weeks in patients chronically treated with benzodiazepines. Patients should be instructed to ingest benzodiazepines before meals and in the absence of antacids because meals and antacids may decrease absorption from the gastrointestinal tract. Chronic administration of benzodiazepines does not adversely affect systemic blood pressure, heart rate, or cardiac rhythm. Although effects on ventilation seem to be absent, it may be prudent to avoid these drugs in patients with chronic lung disease characterized by hypoventilation and/or decreased arterial oxygenation as they may interact with other medications to have adverse effects. Decreased motor coordination and impairment of cognitive function may occur, especially when benzodiazepines are used in combination with other CNS depressant drugs. Acute administration of benzodiazepines may produce transient anterograde amnesia, especially if there is concomitant ingestion of alcohol. For example, there have been reports of profound amnesia in travelers who have ingested triazolam combined with alcohol to facilitate sleep on airline flights.¹⁴⁶

Drug Interactions

Benzodiazepines exert synergistic sedative effects with other CNS depressants including alcohol, inhaled and injected anesthetics, opioids, and α_2 agonists. Anesthetic requirements for inhaled and injected anesthetics are decreased by benzodiazepines. Although benzodiazepines, especially midazolam, potentiate the ventilatory depressant effects of opioids, the analgesic actions of opioids are reduced by benzodiazepines.^{147,148} Indeed, antagonism of benzodiazepine effects with flumazenil results in enhanced analgesic effects of opioids. In patients receiving long-term opioid therapy for chronic pain, all-cause mortality is significantly higher in those receiving opioids and benzodiazepines concurrently.¹⁴⁹

Hypothalamic-Pituitary-Adrenal Axis

Benzodiazepine-induced suppression of the hypothalamic-pituitary-adrenal axis is supported by evidence of suppression of cortisol levels in treated patients.¹⁵⁰ In animals, alprazolam produces dose-dependent inhibition of adrenocorticotropic hormone and cortisol secretion.¹⁵¹ This suppression is enhanced compared with other benzodiazepines and may contribute to the unique efficacy of alprazolam in the treatment of major depression.

Dependence

Even therapeutic doses of benzodiazepines may produce dependence as evidenced by the onset of physical or psychologic symptoms after the dosage is decreased or the drug is discontinued. Symptoms of dependence may occur after more than 6 months of use of commonly prescribed low-potency benzodiazepines. It is misleading to consider dependence as evidence of addiction in the absence of inappropriate drug-seeking behaviors. Withdrawal symptoms (irritability, insomnia, tremulousness) have a time of onset that reflects the elimination half-time of the drug being discontinued. Typically, symptoms of withdrawal appear within 1 to 2 days for short-acting benzodiazepines and within 2 to 5 days for longer acting drugs.

Aging

Aging and liver disease affect glucuronidation less than oxidative metabolic pathways. Lorazepam, oxazepam, and temazepam are metabolized only by glucuronidation and have no active metabolites. For this reason, these benzodiazepines may be preferentially selected in elderly patients over benzodiazepines, such as diazepam, and that is metabolized by hepatic microsomal enzymes to form active metabolites. Elderly patients may also be intrinsically sensitive to benzodiazepines, suggesting that the enhanced response to these drugs that occurs with aging has pharmacodynamic as well as pharmacokinetic components. Long-term benzodiazepine administration may accelerate cognitive decline in elderly patients. Benzodiazepine withdrawal symptoms in the elderly include confusion. Postoperative confusion is more common in elderly long-term benzodiazepine users (daily use for >1 year) than in short-term users or nonusers of benzodiazepines.¹⁵²

Platelet Aggregation

Benzodiazepines may inhibit platelet-activating factor–induced aggregation resulting in drug-induced inhibition of platelet aggregation. Midazolam-induced inhibition of platelet aggregation may reflect conformational changes in platelet membranes.¹⁵³ Although benzodiazepines significantly inhibit platelet aggregation in vitro, they do not appear to affect the risk of hemorrhagic complications in patients with severe, chemotherapy-induced thrombocytopenia¹⁵⁴; the clinical significance of benzodiazepine-induced inhibition of platelet aggregation in the surgical arena is unclear.

Midazolam

Midazolam is a water-soluble benzodiazepine with an imidazole ring in its structure that accounts for stability in aqueous solutions and rapid metabolism.¹⁵⁵ This benzodiazepine has replaced diazepam for use in preoperative medication and conscious sedation. As with other benzodiazepines, the amnestic effects of midazolam are more potent than its sedative effects. Thus, patients may be awake following administration of midazolam but remain amnestic for events and conversations (postoperative instructions) for several hours.

Commercial Preparation

The pK of midazolam is 6.15, which permits the preparation of salts that are water soluble. The parenteral solution of midazolam used clinically is buffered to an acidic pH of 3.5. This is important because midazolam is characterized by a pH-dependent ring-opening phenomenon in which the ring remains open at pH values of less than 4, thus maintaining water solubility of the drug ([Figure 5.11](#)). The ring closes at pH values of greater than 4, as when the drug is exposed to physiologic pH, thus converting midazolam to a highly lipid-soluble drug (see [Figure 5.11](#)). The water solubility of midazolam obviates the need for a solubilizing preparation, such as propylene glycol required for other benzodiazepines that can produce venous irritation or

interfere with absorption after intramuscular (IM) injection. Indeed, midazolam causes minimal to no discomfort during or after IV or IM injection. Midazolam is compatible with lactated Ringer solution and can be mixed with the acidic salts of other drugs, including opioids and anticholinergics.

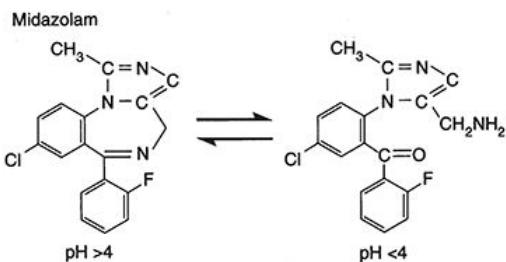


FIGURE 5.11 Reversible ring opening of midazolam above and below a pH of 4. The ring closes at a pH greater than 4, converting midazolam from a water-soluble to a lipid-soluble drug.

Pharmacokinetics

Midazolam undergoes rapid absorption from the gastrointestinal tract and prompt passage across the blood-brain barrier. Despite this prompt passage into the brain, midazolam is considered to have a relatively slow effect-site equilibration time (0.9–5.6 minutes) compared with other drugs such as propofol and thiopental. In this regard, IV doses of midazolam should be sufficiently spaced to permit the peak clinical effect to be appreciated before a repeat dose is considered. Only about 50% of an orally administered dose of midazolam reaches the systemic circulation, reflecting a substantial first-pass hepatic effect. As for most benzodiazepines, midazolam is extensively bound to plasma proteins; this binding is independent of the plasma concentration of midazolam ([Table 5.2](#)).^{155,156} The short duration of action of a single dose of midazolam is due to its lipid solubility, leading to rapid redistribution from the brain to inactive tissue sites as well as rapid hepatic clearance.

TABLE 5.2

Comparative pharmacology of benzodiazepines

	Equivalent dose (mg)	Volume of distribution (L/kg)	Protein binding (%)	Clearance (mL/kg/minute)	Elimination half-time (hour)
Midazolam	0.15-0.3	1.0-1.5	96-98	6-8	1-4
Diazepam	0.3-0.5	1.0-1.5	96-98	0.2-0.5	1-37
Lorazepam	0.05	0.8-1.3	96-98	0.7-1.0	10-20

The elimination half-time of midazolam is 1 to 4 hours, which is much shorter than that of diazepam (see [Table 5.2](#)).¹⁵⁵ The elimination half-time may be doubled in elderly patients, reflecting age-related decreases in hepatic blood flow and possibly enzyme activity. The V_d of midazolam and diazepam are similar, probably reflecting their similar lipid solubility and high degree of protein binding. Elderly and morbidly obese patients have an increased V_d of midazolam resulting from enhanced distribution of the drug into peripheral adipose tissues. The clearance of midazolam is more rapid than that of diazepam, as reflected by the context-sensitive half-time. As a result of these differences, the CNS effects of midazolam would be expected to be shorter than those of diazepam. Indeed, tests of mental function return to normal within 4 hours after the administration of midazolam in healthy young patients.

The institution of cardiopulmonary bypass is associated with a decrease in the plasma concentration of midazolam and an increase on termination of cardiopulmonary bypass.²⁶ These changes are attributed to redistribution of priming fluid into body tissues. In addition, benzodiazepines are extensively bound to protein, and changes in protein concentrations and pH that accompany institution and termination of cardiopulmonary bypass may have significant effects on the unbound and pharmacologically active fractions of these drugs. The elimination half-time of midazolam is prolonged after cardiopulmonary bypass.

Metabolism

Midazolam is rapidly metabolized by hepatic and small intestine cytochrome P450 (CYP3A4) enzymes to active and inactive metabolites (**Figure 5.12**).¹⁵⁵ The principal metabolite of midazolam, 1-hydroxymidazolam, has approximately half the activity of the parent compound.¹⁵⁷ This active metabolite is rapidly conjugated to 1-hydroxymidazolam glucuronide and is subsequently cleared by the kidneys. This glucuronide metabolite has substantial pharmacologic activity when present in high concentrations, as may occur in critically ill patients with renal insufficiency who are receiving continuous IV infusions of midazolam over prolonged periods of time. In these patients, the glucuronide metabolite may have synergistic sedative effects with the parent compound.¹⁵⁸ The other pharmacologically active metabolite of midazolam, 4-hydroxymidazolam, is not present in detectable concentrations in the plasma following IV administration of midazolam.

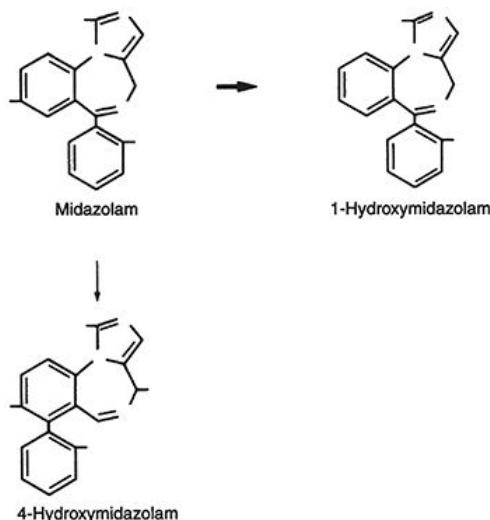


FIGURE 5.12 The principal metabolite of midazolam is 1-hydroxymidazolam. A lesser amount of midazolam is metabolized to 4-hydroxymidazolam. Reprinted with permission from Reves JG, Fragen RJ, Vinik HR, et al. *Midazolam: pharmacology and uses*. Anesthesiology. 1985;62(3):310-324. Copyright © 1985 American Society of Anesthesiologists, Inc.

Metabolism of midazolam is slowed in the presence of drugs (cimetidine, erythromycin, calcium channel blockers, antifungal drugs) that inhibit cytochrome P450 enzymes resulting in unexpected CNS depression.¹⁵⁹ Cytochrome P450 3A enzymes also influence the metabolism of fentanyl. In this regard, the hepatic clearance of midazolam is inhibited by fentanyl as administered during general anesthesia.¹⁶⁰ Overall, the hepatic clearance rate of midazolam is 5 times greater than that of lorazepam and 10 times greater than that of diazepam.

Renal Clearance

The elimination half-time, V_d , and clearance of midazolam are not altered by renal failure.¹⁶¹ This is consistent with the extensive hepatic metabolism of midazolam.

Effects on Organ Systems

Central Nervous System

Midazolam, like other benzodiazepines, produces decreases in CMRO₂ and cerebral blood flow analogous to barbiturates and propofol. Midazolam causes dose-related changes in regional cerebral blood flow in brain regions associated with the normal functioning of arousal, attention, and memory.¹⁶² Cerebral vasomotor responsiveness to carbon dioxide is preserved during midazolam anesthesia.⁴⁸ Patients with decreased intracranial compliance show little or no change in ICP when given midazolam doses of 0.15 to 0.27 mg/kg

IV. Thus, midazolam is an acceptable alternative to barbiturates for induction of anesthesia in patients with intracranial pathology. There is some evidence, however, that patients with severe head trauma but ICP of less than 18 mm Hg may experience an undesirable increase in ICP when midazolam (0.15 mg/kg IV) is administered rapidly (**Figure 5.13**).¹⁶³ Similar to thiopental, induction of anesthesia with midazolam does not prevent increases in ICP associated with direct laryngoscopy for tracheal intubation.¹⁶⁴ Although midazolam may improve neurologic outcome after incomplete ischemia, benzodiazepines have not been shown to possess neuroprotective activity in humans. Midazolam is a potent anticonvulsant effective in the treatment of status epilepticus. Prolonged sedation of infants in critical care units (4–11 days) with midazolam and fentanyl has been associated with encephalopathy on withdrawal of the benzodiazepine.¹⁶⁵ Paradoxical excitement occurs in less than 1% of all patients receiving midazolam and is effectively treated with a specific benzodiazepine antagonist, flumazenil.¹⁶⁶

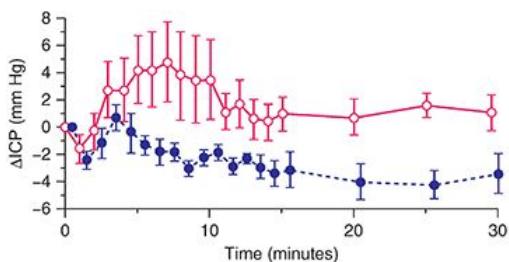


FIGURE 5.13 Administration of midazolam, 0.15 mg/kg IV, to patients with severe head injury (Glasgow Coma Scale score ≤ 6) was associated with an increase in intracranial pressure (ICP) when the control ICP was less than 18 mm Hg (open circles) but not when the control ICP was ≥ 18 mm Hg or greater (closed circles). Reprinted from Papazian L, Albanese J, Thirion X, et al. Effect of bolus doses of midazolam on intracranial pressure and cerebral perfusion pressure in patients with severe head injury. Br J Anaesth. 1993;71(2):267-271. Copyright © 1993 Elsevier. With permission.

Ventilation

Midazolam produces dose-dependent decreases in ventilation with 0.15 mg/kg IV producing effects similar to diazepam, 0.3 mg/kg IV.¹⁶⁷ Patients with chronic obstructive pulmonary disease experience even greater midazolam-induced depression of ventilation.¹⁶⁸ Transient apnea may occur after rapid injection of large doses of midazolam (>0.15 mg/kg IV), especially in the presence of preoperative medication that includes an opioid.¹⁶⁹ In healthy volunteers, midazolam alone produced no ventilatory depressant effects, whereas the combination of midazolam, 0.05 mg/kg IV, and fentanyl, 2 μ g/kg IV, resulted in arterial hypoxemia and/or hypoventilation.¹⁷⁰ Midazolam, 0.05 or 0.075 mg/kg IV, was shown to depress resting ventilation in healthy volunteers, whereas spinal anesthesia (mean sensory level T6) stimulated resting ventilation, and the combination had a modest synergistic effect for depressing resting ventilation.¹⁷¹ Benzodiazepines also depress the swallowing reflex and decrease upper airway activity.

Cardiovascular System

Historically, large IV doses of midazolam were tested for use as an anesthetic induction agent. The use of midazolam never gained widespread use; loss of consciousness, even with high doses, is slow and unreliable, and hemodynamic response to endotracheal intubation is not reliably blunted. Midazolam, 0.2 mg/kg IV, for induction of anesthesia produces a greater decrease in systemic blood pressure and increase in heart rate than does diazepam, 0.5 mg/kg IV.¹⁷² Conversely, these midazolam-induced hemodynamic changes are similar to the changes produced by thiopental, 3 to 4 mg/kg IV.¹⁷³ Cardiac output is not altered by midazolam, suggesting that blood pressure changes are due to decreases in systemic vascular resistance. In this regard, benzodiazepines may be beneficial in improving cardiac output in the presence of congestive heart failure. In the presence of hypovolemia, administration of midazolam results in enhanced blood pressure–lowering effects similar to those produced by other IV induction drugs.¹⁷⁴ Midazolam does not prevent blood pressure

and heart rate responses evoked by intubation of the trachea. In fact, this mechanical stimulus may offset the blood pressure–lowering effects of large doses of midazolam administered IV. The effects of midazolam on systemic blood pressure are directly related to the plasma concentration of the benzodiazepine. However, a plateau plasma concentration appears to exist (ceiling effect) above which little further change in systemic blood pressure occurs.

Clinical Uses

Preoperative Medication

Midazolam is the most commonly used oral preoperative medication for children. Oral midazolam syrup (2 mg/mL) is effective for producing sedation and anxiolysis at a dose of 0.25 mg/kg with minimal effects on ventilation and oxygen saturation even when administered at doses as large as 1 mg/kg (maximum, 20 mg).¹⁷⁵ Midazolam, 0.5 mg/kg administered orally 30 minutes before induction of anesthesia, provides reliable sedation and anxiolysis in children without producing delayed awakening (**Figure 5.14**).¹⁷⁶ Use of oral midazolam to produce mild to moderate sedation in children before surgery remains common¹⁷⁷; recent comparative studies suggest that oral dexmedetomidine produces similar sedation while reducing emergence delirium.¹⁷⁸ Although it is recommended that oral midazolam be administered at least 20 minutes before surgery, there is evidence that significant anterograde amnesia is present when 0.5 mg/kg orally is administered 10 minutes before surgery.¹⁷⁹ Midazolam crosses the placenta, but the fetal-to-maternal ratio is significantly less than that for other benzodiazepines.

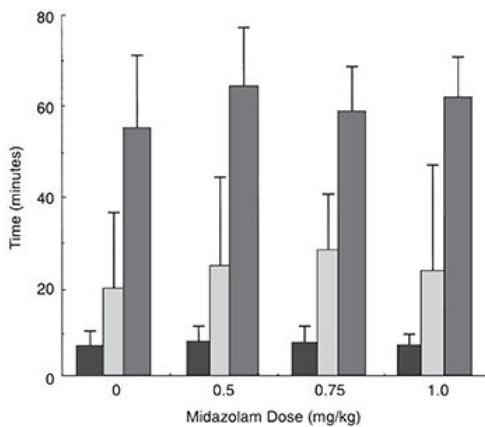


FIGURE 5.14 Increasing doses of oral midazolam premedication administered 30 minutes before the induction of anesthesia did not produce different effects on the interval from the end of surgery until transported to the postanesthesia care unit (solid bars), interval from arrival in the postanesthesia care unit until spontaneous eye opening (light gray bars), and time in the postanesthesia care unit (dark gray bars). *Reprinted by permission from Springer: McMillan CO, Spahr-Schopfer IA, Sikich N, et al. Premedication of children with oral midazolam. Can J Anaesth. 1992;39(6):545-550. Copyright © 1992 Canadian Anesthesiologists.*

Intravenous Sedation

Midazolam in doses of 1.0 to 2.5 mg IV (onset within 30-60 seconds, time to peak effect 3-5 minutes, duration of sedation 15-80 minutes) is effective for sedation during regional anesthesia as well as for brief therapeutic procedures. The effect-site equilibrium time for midazolam must be considered in recognizing the likely time of peak clinical effect and the need for supplemental doses of midazolam.

The most significant side effect of midazolam when used for sedation is depression of ventilation caused by a decrease in the hypoxic drive, particularly in concert with other anesthetic drugs. Midazolam-induced depression of ventilation is exaggerated (synergistic effects) in the presence of opioids and other CNS depressant drugs.¹⁴⁸ Patients with chronic obstructive pulmonary disease may also manifest exaggerated

depression of ventilation following administration of benzodiazepines to produce sedation. It is important to appreciate that increasing age greatly increases pharmacodynamic variability and is associated with generally increased sensitivity to the hypnotic effects of midazolam.¹⁸⁰

Induction of Anesthesia

Although seldom used for this purpose currently, anesthesia can be induced by administration of midazolam, 0.1 to 0.2 mg/kg IV, over 30 to 60 seconds. Nevertheless, thiopental usually produces induction of anesthesia 50% to 100% faster than midazolam (Figure 5.15).¹⁸¹ Onset of unconsciousness (synergistic interaction) is facilitated when a small dose of opioid (fentanyl, 50-100 µg IV or its equivalent) precedes the injection of midazolam by 1 to 3 minutes. The dose of midazolam required for the IV induction of anesthesia is also less when preoperative medication includes a CNS depressant drug. In healthy patients receiving small doses of benzodiazepines, the cardiovascular depression associated with these drugs is minimal. When significant cardiovascular responses occur, it is most likely a reflection of benzodiazepine-induced peripheral vasodilation. As with depression of ventilation, cardiovascular changes produced by benzodiazepines may be exaggerated in the presence of other CNS depressant drugs such as propofol and thiopental.

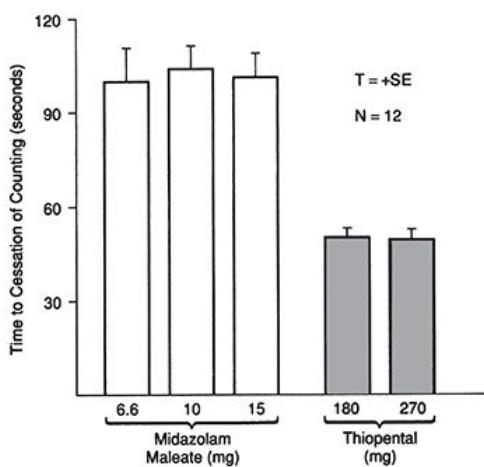


FIGURE 5.15 Induction of anesthesia as depicted by time to cessation of counting occurs in about 110 seconds after the intravenous administration of midazolam compared with about 50 seconds after injection of thiopental. Reprinted with permission from Sarnquist FH, Mathers WD, Brock-Utne J, et al. A bioassay of water-soluble benzodiazepine against sodium thiopental. *Anesthesiology*. 1980;52(2):149-153. Copyright © 1980 American Society of Anesthesiologists, Inc.

Maintenance of Anesthesia

Midazolam may be administered to supplement opioids, propofol, and/or inhaled anesthetics during maintenance of anesthesia. The context-sensitive half-time for midazolam increases modestly with an increasing duration of administration of a continuous infusion of this benzodiazepine.¹⁹ Anesthetic requirements for volatile anesthetics are decreased in a dose-dependent manner by midazolam. Awakening after general anesthesia that includes induction of anesthesia with midazolam is 1.0 to 2.5 times longer than that observed when thiopental is used for the IV induction of anesthesia.¹⁸² Gradual awakening in patients who receive midazolam is rarely associated with nausea, vomiting, or emergence excitement.

Postoperative Sedation

Long-term IV administration of midazolam (loading dose 0.5-4 mg IV and maintenance dose 1-7 mg/hour IV) to produce sedation in intubated patients results in relative saturation of peripheral tissues with midazolam and clearance from the systemic circulation becomes less dependent on redistribution into peripheral tissues and more dependent on hepatic metabolism.¹⁸³ In addition, pharmacologically active

metabolites may accumulate with prolonged IV administration of the parent drug. Under these conditions, plasma concentrations of midazolam decrease more slowly (emergence delayed) after discontinuation of the IV infusion compared with single IV injections. Emergence time is also a function of the plasma concentrations of midazolam at the time the IV infusion is discontinued. Patients maintained at higher plasma concentrations of midazolam take longer to awaken than patients maintained at lower plasma concentrations for comparable periods of time. The concomitant administration of analgesic doses of opioids greatly decreases the needed dose of midazolam and results in a more rapid recovery from sedation following discontinuation of the IV infusion of midazolam.¹⁸³ Emergence time from midazolam infusion is increased in elderly patients, obese patients, and in the presence of severe liver disease.

Paradoxical Vocal Cord Motion

Paradoxical vocal cord motion is a cause of nonorganic upper airway obstruction and stridor that may manifest postoperatively. Midazolam 0.5 to 1 mg IV may be an effective treatment for paradoxical vocal cord motion.¹⁸⁴

Diazepam

Diazepam is a highly lipid-soluble benzodiazepine with a more prolonged duration of action compared with midazolam. Because of the beneficial aspects of midazolam pharmacology, parenteral diazepam is seldom used as part of current anesthetic regimens.

Commercial Preparation

Diazepam is dissolved in organic solvents (propylene glycol, sodium benzoate) because it is insoluble in water. The solution is viscid, with a pH of 6.6 to 6.9. Dilution with water or saline causes cloudiness but does not alter the potency of the drug. Injection by either the IM or IV route may be painful. Diazepam is also available in a unique soybean formulation for IV injection. This formulation is associated with a lower incidence of pain on injection and thrombophlebitis.

Diazepam is rapidly absorbed from the gastrointestinal tract after oral administration with bioavailability nearing 100%, reaching peak concentrations in about 1 hour in adults but as quickly as 15 to 30 minutes in children. There is rapid uptake of diazepam into the brain, followed by redistribution to inactive tissue sites, especially fat, as this benzodiazepine is highly lipid soluble. The V_d of diazepam is large, reflecting extensive tissue uptake of this lipid-soluble drug (see [Table 5.2](#)). Women, with a greater body fat content, are likely to have a larger V_d for diazepam than men. Diazepam rapidly crosses the placenta, achieving fetal concentrations equal to and sometimes greater than those present in the maternal circulation.¹⁸⁵

Protein Binding

The protein binding of benzodiazepines parallels their lipid solubility. As such, highly lipid-soluble diazepam is extensively bound, presumably to albumin (see [Table 5.2](#)). Cirrhosis of the liver or renal insufficiency, with associated decreases in plasma concentrations of albumin, may manifest as decreased protein binding of diazepam and an increased incidence of drug-related side effects.¹⁸⁶ The high degree of protein binding limits the efficacy of hemodialysis in the treatment of diazepam overdose.

Metabolism

Diazepam is principally metabolized by hepatic microsomal enzymes using an oxidative pathway of *N*-demethylation. The two principal metabolites of diazepam are desmethyldiazepam and oxazepam, with a lesser amount metabolized to temazepam ([Figure 5.16](#)). Desmethyldiazepam is metabolized more slowly than oxazepam and is only slightly less potent than diazepam. Therefore, it is likely that this metabolite contributes to the return of drowsiness that manifests 6 to 8 hours after administration of diazepam as well as to sustained effects usually attributed to the parent drug. Alternatively, enterohepatic recirculation may contribute to recurrence of sedation.¹⁸⁷ The plasma concentration of diazepam at this time is clinically insignificant and probably reflects its rapid removal as a conjugate of glucuronic acid. Ultimately,

desmethyl diazepam is excreted in urine in the form of oxidized and glucuronide conjugated metabolites. Unchanged, diazepam is not appreciably excreted in urine.

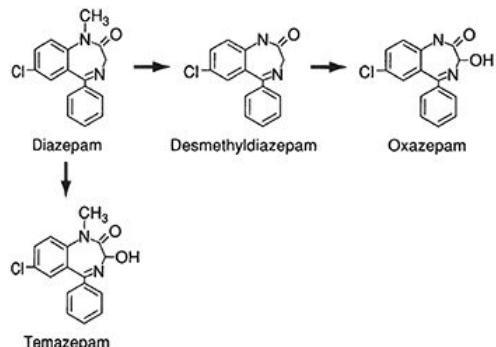


FIGURE 5.16 The principal metabolites of diazepam are desmethyldiazepam and oxazepam. A lesser amount of diazepam is metabolized to temazepam.

Elimination Half-Time

The elimination half-time of diazepam is ranges from 21 to 37 hours in healthy volunteers (see [Table 5.2](#)). Cirrhosis of the liver is accompanied by up to fivefold increases in the elimination half-time of diazepam.¹⁸⁸ Likewise, the elimination half-time of diazepam increases progressively with increasing age, which contributes to the increased sensitivity of these patients to the drug's sedative effects.¹⁸⁸ Prolongation of the elimination half-time of diazepam in the presence of cirrhosis of the liver is due to decreased protein binding of the drug, leading to an increased V_d . In addition, hepatic clearance of diazepam is likely to be decreased, reflecting decreased hepatic blood flow characteristic of cirrhosis of the liver. Compared with lorazepam, diazepam has a longer elimination half-time but shorter duration of action because it dissociates more rapidly than lorazepam from GABA_A receptors, permitting more rapid redistribution to inactive tissue sites.

Desmethyl diazepam, the principal metabolite of diazepam, has an elimination half-time of 48 to 96 hours. As such, the elimination half-time of the metabolite may exceed that of the parent drug. Plasma concentrations of diazepam often decline more rapidly than plasma concentrations of desmethyl diazepam. This pharmacologically active metabolite can accumulate in plasma and tissues during chronic use of diazepam. Prolonged somnolence associated with high doses of diazepam is likely to be caused by sequestration of the parent drug and its active metabolite, desmethyl diazepam, in tissues, presumably fat, for subsequent release back into the circulation. A week or more is often required for elimination of these compounds from plasma after discontinuation of chronic diazepam therapy.

Effects on Organ Systems

Diazepam, like other benzodiazepines, produces significant effects on ventilation and minimal effects on the systemic circulation. Hepatic and renal functions are not altered appreciably. Diazepam does not increase the incidence of nausea and vomiting. There is no change in the circulating plasma concentrations of stress-responding hormones (catecholamines, arginine vasopressin, cortisol).

Ventilation

Diazepam produces minimal depressant effects on ventilation, with detectable increases in Paco_2 not occurring until 0.2 mg/kg IV is administered. This slight increase in Paco_2 is due primarily to a decrease in tidal volume. Nevertheless, rarely, small doses of diazepam (<10 mg IV) have produced apnea.¹⁸⁹ Combination of diazepam with other CNS depressants (opioids, alcohol) or administration of this drug to patients with chronic obstructive airway disease may result in exaggerated or prolonged depression of ventilation. The slope of the line depicting the ventilatory response to carbon dioxide is decreased nearly 50% within 3 minutes after the administration of diazepam, 0.4 mg/kg IV (Figure 5.17).¹⁹⁰ This depression of the

slope persists for about 25 minutes and parallels the level of consciousness. Despite the decrease in slope, the carbon dioxide response curve is not shifted to the right as observed with depression of ventilation produced by opioids. These depressant effects on ventilation seem to be a CNS effect because the mechanics of respiratory muscles are unchanged.

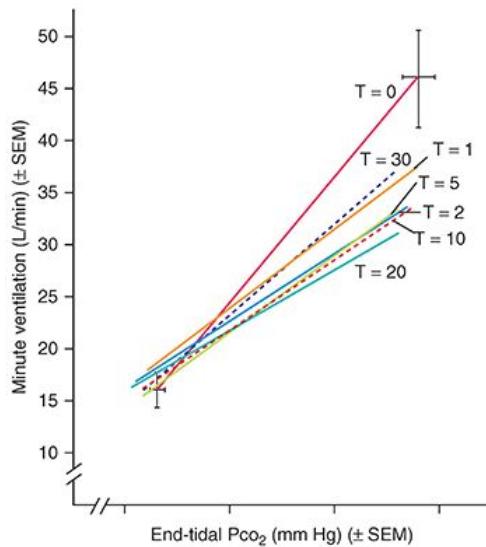


FIGURE 5.17 The slope of the line depicting the ventilatory response to carbon dioxide is decreased ($T = \text{minutes}$) following administration of diazepam, 0.4 mg/kg intravenously. Abbreviation: SEM, standard error of the mean. Reprinted with permission from Gross JB, Smith L, Smith TC. Time course of ventilatory response to carbon dioxide after intravenous diazepam. Anesthesiology. 1982;57(1):18-21. Copyright © 1982 American Society of Anesthesiologists, Inc.

Cardiovascular System

Diazepam administered in doses of 0.5 to 1 mg/kg IV for induction of anesthesia typically produces minimal decreases in systemic blood pressure, cardiac output, and systemic vascular resistance that are similar in magnitude to those observed during natural sleep (10%-20% decreases) (Table 5.3).¹⁹¹ Because of its relative hemodynamic stability, high-dose diazepam was once used for cardiac surgery. There is a transient depression of baroreceptor-mediated heart rate responses that is less than the depression evoked by volatile anesthetics but that could, in hypovolemic patients, interfere with optimal compensatory changes.¹⁹² In patients with increased left ventricular end-diastolic pressure, a small dose of diazepam significantly decreases this pressure. Diazepam appears to have no direct action on the sympathetic nervous system, and it does not cause orthostatic hypotension.

TABLE 5.3

Cardiovascular effects of diazepam (0.5 mg/kg intravenously) and diazepam-nitrous oxide^a

	Awake	Diazepam	Diazepam-nitrous oxide
Systolic blood pressure (mm Hg)	144	125 ^a	121 ^a
Diastolic blood pressure (mm Hg)	81	74	75
Mean arterial pressure (mm Hg)	102	91 ^a	91 ^a
Heart rate (beats per minute)	66	68	65
Pulmonary artery pressure (mm Hg)	18.4	16.3	17.2
Pulmonary artery occlusion pressure (mm Hg)	11.5	10.6	11.9
Cardiac output (L per minute)	5.3	5.1	4.8 ^a
	1,391	1,344	1,377

Systemic vascular resistance (dynes/second/cm⁻⁵)

**P* < .05 compared with the awake value.

^aReprinted with permission from McCammon RL, Hilgenberg JC, Stoelting RK. Hemodynamic effects of diazepam and diazepam-nitrous oxide in patients with coronary artery disease. *Anesth Analg*. 1980;59(6):438-441. Copyright © 1980 International Anesthesia Research Society.

Skeletal Muscle

Skeletal muscle relaxant effects reflect actions of diazepam on spinal internuncial neurons and not actions at the neuromuscular junction.¹⁹³ Presumably, diazepam diminishes the tonic facilitatory influence on spinal γ neurons, and thus, skeletal muscle tone is decreased. Tolerance occurs to the skeletal muscle relaxant effects of benzodiazepines.

Overdose

A CNS intoxication can be expected at diazepam plasma concentrations of greater than 1,000 ng/mL. Despite massive overdoses of diazepam, serious sequelae are unlikely to occur if cardiac and pulmonary functions are supported and other drugs such as alcohol are not present.

Clinical Uses

Diazepam remains a popular oral drug for preoperative medication of adults and has been recommended for treatment of local anesthetic-induced seizures. Both diazepam and lorazepam are commonly used benzodiazepines for management of delirium tremens.¹⁹⁴ Production of skeletal muscle relaxation by diazepam is often used in the management of lumbar disc disease and may be of value in the rare patient who develops tetany. Midazolam has largely replaced diazepam for IV sedation and the preoperative medication of children.

Anticonvulsant Activity

The prior administration of diazepam, 0.25 mg/kg IV, to animals protects against the development of seizures due to local anesthetic toxicity. Evidence for this protection is an increased convulsant dose of lidocaine in benzodiazepine-pretreated animals (**Figure 5.18**).¹⁹⁵ Diazepam, 0.1 mg/kg IV, is effective in abolishing seizure activity produced by lidocaine, delirium tremens, and status epilepticus.

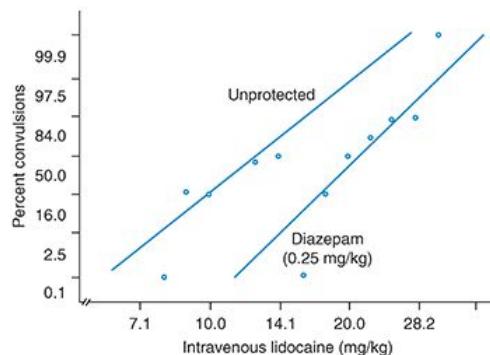


FIGURE 5.18 Prior administration of diazepam, 0.25 mg/kg intravenously, increases the intravenous dose of lidocaine required to produce seizures compared with untreated (unprotected) animals. *Reprinted with permission from De Jong RH, Heavner JE. Diazepam prevents and aborts lidocaine convulsions in monkeys. Anesthesiology. 1974;41(3):226-230. Copyright © 1974 American Society of Anesthesiologists, Inc.*

The efficacy of diazepam as an anticonvulsant may reflect its ability to facilitate the actions of the inhibitory neurotransmitter GABA. In contrast to barbiturates, which inhibit seizures by nonselective depression of the CNS, diazepam selectively inhibits activity in the limbic system, particularly the

hippocampus. If diazepam is administered to terminate seizures, a longer acting antiepileptic drug such as fosphenytoin is also administered.

Lorazepam

Lorazepam resembles oxazepam, differing only in the presence of an extra chloride atom on the ortho position of the 5-phenyl moiety. Lorazepam is a more potent sedative and amnesic than midazolam and diazepam, with a duration of action intermediate between the other two agents. Its effects on ventilation, the cardiovascular system, and skeletal muscles resemble those of other benzodiazepines.

Pharmacokinetics

Lorazepam is conjugated with glucuronic acid in the liver to form pharmacologically inactive metabolites that are excreted by the kidneys. This contrasts with formation of pharmacologically active metabolites after the administration of midazolam and diazepam. The elimination half-time is 10 to 20 hours, with urinary excretion of lorazepam glucuronide accounting for greater than 80% of the injected dose (see [Table 5.2](#)). Compared with midazolam, lorazepam has a much slower metabolic clearance. This may be explained by the slower hepatic glucuronidation of lorazepam compared with more rapid oxidative hydroxylation of midazolam. Because formation of glucuronide metabolites of lorazepam is not entirely dependent on hepatic microsomal enzymes, the metabolism of lorazepam is less likely than that of diazepam to be influenced by alterations in hepatic function, increasing age, or drugs that inhibit P450 enzymes such as cimetidine. The elimination half-time of lorazepam is not prolonged in elderly patients or in those treated with cimetidine. Lorazepam has a slower onset of action than midazolam or diazepam because of its lower lipid solubility and slower entrance into the CNS.

Clinical Uses

Lorazepam undergoes reliable absorption after oral and IM injection, which contrasts with diazepam. After oral administration, maximal plasma concentrations of lorazepam occur in 2 to 4 hours and persist at therapeutic levels for up to 24 to 48 hours. The recommended oral dose of lorazepam for preoperative medication is 50 µg/kg, not to exceed 4 mg.¹⁹⁶ With this dose, maximal anterograde amnesia lasting up to 6 hours occurs, and sedation is not excessive. Larger oral doses produce additional sedation without increasing amnesia. The prolonged duration of action of lorazepam limits its usefulness for preoperative medication when rapid awakening at the end of surgery is desirable.

After a single IV dose (1-4 mg), the onset of effect occurs within 1 to 2 minutes, with a time-to-peak effect of 20 to 30 minutes, and a duration of sedative effects ranging from 6 to 10 hours.¹⁹⁷ Infusions of lorazepam to produce postoperative sedation result in significant delays in emergence from sedation compared with midazolam.¹⁸³ Obesity prolongs the sedative effects of lorazepam reflecting the larger V_d and longer elimination half-time.

A slow onset limits the usefulness of lorazepam for (1) IV induction of anesthesia, (2) IV sedation during regional anesthesia, or (3) use as an anticonvulsant. Like diazepam, lorazepam is effective in limiting the incidence of emergence reactions after administration of ketamine. Although it is insoluble in water and thus requires use of solvents such as polyethylene glycol or propylene glycol, lorazepam is alleged to be less painful on injection and to produce less venous thrombosis than diazepam.

Temazepam

Temazepam is an orally active benzodiazepine administered exclusively for the treatment of insomnia. Oral absorption is complete, but peak plasma concentrations do not reliably occur until about 2.5 hours after its administration. Metabolism in the liver results in weakly active to inactive metabolites that are conjugated with glucuronic acid. The elimination half-time is about 15 hours. Temazepam, 15 to 30 mg orally, does not alter the proportion of rapid eye movement sleep to total sleep in adults. Despite the relatively long elimination half-time, temazepam, as used to treat insomnia, is unlikely to be accompanied by residual drowsiness the following morning. Tolerance or signs of withdrawal do not occur, even after nightly administration for 30 consecutive days.

Remimazolam

Remimazolam is a new ultrashort acting benzodiazepine derivative. It is a carboxylic acid ester that, like remifentanil, is rapidly metabolized by nonspecific tissue esterases to an inactive carboxylic acid.¹⁹⁸ Remimazolam is a high-affinity and selective ligand for the benzodiazepine site of the GABA_A receptor. The drug is currently under development for FDA approval for the indication of anesthetic/sedative in gastrointestinal or pulmonary procedures. Recent studies show that full alertness after a short diagnostic procedure (bronchoscopy) was more rapid after remimazolam than after midazolam (6.0 vs 12 minutes).¹⁹⁹

Flumazenil

Flumazenil, a 1,4-imidazobenzodiazepine derivative, is a specific and exclusive benzodiazepine antagonist with a high affinity for benzodiazepine receptors, where it exerts minimal agonist activity.^{200 201} As a competitive antagonist, flumazenil prevents or reverses, in a dose-dependent manner, all the agonist effects of benzodiazepines. Flumazenil also effectively antagonizes the benzodiazepine component of ventilatory depression that is present during combined administration of a benzodiazepine and opioid.¹⁴⁸ Metabolism of flumazenil is by hepatic microsomal enzymes to inactive metabolites.

Dose and Administration

The dose of flumazenil should be titrated individually to obtain the desired level of consciousness. The recommended initial dose is 0.2 mg IV (8-15 µg/kg IV), which typically reverses the CNS effects of benzodiazepine agonists within about 2 minutes. If required, further doses of 0.1 mg IV (to a total of 1 mg IV) may be administered at 60-second intervals. Generally, total doses of 0.3 to 0.6 mg IV have been adequate to decrease the degree of sedation to the required extent in patients sedated or anesthetized with benzodiazepines, whereas total doses of 0.5 to 1.0 mg IV are usually sufficient to completely abolish the effect of a therapeutic dose of a benzodiazepine. In patients who are unconscious due to an overdose with an unknown drug or drugs, failure to respond to IV doses of flumazenil of more than 5 mg probably indicates the involvement of intoxicants other than benzodiazepines or the presence of functional organic disorders. The duration of action of flumazenil is 30 to 60 minutes, and supplemental doses of the antagonist may be needed to maintain the desired level of consciousness. An alternative to repeated doses of flumazenil to maintain wakefulness is a continuous low-dose infusion of flumazenil, 0.1 to 0.4 mg per hour.²⁰⁰ The administration of flumazenil to patients being treated with antiepileptic drugs for control of seizure activity is not recommended as it could precipitate acute withdrawal seizures.²⁰²

Side Effects

Flumazenil-induced antagonism of excess benzodiazepine agonist effects is not followed by acute anxiety, hypertension, tachycardia, or neuroendocrine evidence of a stress response in postoperative patients.^{203 204} Reversal of benzodiazepine agonist effects with flumazenil is not associated with alterations in left ventricular systolic function or coronary hemodynamics in patients with coronary artery disease.²⁰⁵ The weak intrinsic agonist activity of flumazenil most likely attenuates evidence of abrupt reversal of agonist effects. Flumazenil does not alter anesthetic requirements (minimum alveolar concentration [MAC]) for volatile anesthetics, suggesting that these drugs do not exert any of their depressant effects on the CNS at GABA_A receptors.²⁰⁶ Flumazenil, administered at about 10 times the clinically recommended dose, has no agonist effects on resting ventilation or psychomotor performance in normal individuals.²⁰⁷

Short-Acting Nonbenzodiazepine Benzodiazepines

Benzodiazepine refers to a specific chemical structure consisting of a benzene ring and a diazepine ring, hence the name benzodiazepine. Unfortunately, the name has also come to refer to a pharmacologic class of drugs with a shared clinical activity and a shared molecular binding site on the GABA_A receptor at the interface between the α and γ subunits, the benzodiazepine site. Eventually, drugs were found that bound to the same receptor, and exhibited the same pharmacology, but did not consist of a benzene ring bound to a diazepine ring. These drugs were given the cumbersome but vaguely amusing name: nonbenzodiazepine

benzodiazepine. The agents that have been approved are zaleplon (Sonata), zolpidem (Ambien), and more recently eszopiclone (Lunesta).

Zaleplon, zolpidem, and eszopiclone exert activity at the GABA receptor complex.²⁰⁸ These drugs seem to have more selectivity for certain subunits of GABA receptors, resulting in a clinical profile for treatment of sleeping disorders that is more efficacious with fewer side effects than occur with conventional benzodiazepines. Their use has steadily risen during the past decade, with 3% of Americans now reporting use of one or more of these agents during the prior month.²⁰⁹ Due to variations in binding to GABA receptor subunits, these drugs show differences in their effect on sleep stages. Zaleplon (10 mg orally) has a rapid elimination, so there are few residual side effects after taking a single dose at bedtime. It may be particularly useful for patients with delayed onset of sleep. By comparison, zolpidem (10 mg orally) has a delayed elimination, prolonging drug effect. This may result in residual sedation and side effects but may be used for sustained treatment of insomnia with less waking during the night. All of these agents are slightly effective for insomnia, but their overall effects are of questionable clinical importance.²¹⁰

Barbiturates

The introduction of thiopental in 1934 revolutionized the practice of anesthesia. This rapid-acting barbiturate made it possible to induce general anesthesia in seconds, avoiding a slow, often unpleasant, more dangerous induction with diethyl ether. Thiopental and other barbiturate sedative-hypnotics were imported from manufacturers overseas, but these companies have now ceased exporting barbiturates to the United States in order to protest their use as a part of the lethal injection “cocktail” for capital punishment.²¹¹ We still include a discussion of barbiturate pharmacology in this chapter, and this is done for several reasons: First, it is conceivable that shipments of these drugs may resume. Second, some anesthesiologists who practice outside of the United States use these drugs. Most importantly, the pharmacokinetics and pharmacodynamics of barbiturates are the prototypes and comparators for almost all of our clinically used IV anesthetics. To understand the literature on drugs like propofol, etomidate, and midazolam, it is critical to know the properties of barbiturates to which they were often compared, as these were the gold standard during their development.

Barbiturates' Use in Anesthesia

The clinically used barbiturates are derived from barbituric acid. The substitutions on this molecule determine the physicochemical properties, pharmacokinetics, and the relative potency to produce various effects. Oxybarbiturates (pentobarbital, secobarbital) have oxygen at the second position. Replacement of the oxygen with a sulfur atom results in the corresponding thiobarbiturates (thiopental, thiamylal), which are much more lipid soluble and have greater hypnotic potency. A phenyl group at the fifth position (phenobarbital) increases the anticonvulsant, but not hypnotic, potency. On the other hand, a methyl group on the nitrogen (as with methohexitol) increases hypnotic potency but lowers the seizure threshold and causes myoclonus during induction.

Mechanism of Action

Barbiturates are one of the earliest examples of CNS depressants that act in part by potentiating GABA_A channel activity. At clinically used concentrations, they also act on glutamate, adenosine, and neuronal nicotinic acetylcholine receptors. Studies in knock-in mice have shown that GABA_A receptors containing β₃ subunits are responsible for the immobilizing activity of pentobarbital and partly responsible for the hypnotic activity.²¹² The interaction of barbiturates (as well as propofol and etomidate acting at different sites) functions allosterically to increase the affinity of GABA for its binding site, thereby increasing the duration of the GABA_A-activated opening of chloride channels (see **Figure 5.10**). Barbiturates can also mimic the action of GABA by directly activating GABA_A receptors at higher doses.

Pharmacokinetics

Thiopental causes rapid onset and rapid awakening after a single IV dose due to rapid uptake then rapid redistribution out of the brain into inactive tissues (**Figure 5.19**).²¹³ As previously discussed, this is the basis for the short action of most other highly lipophilic drugs. Ultimately, elimination from the body depends almost entirely on metabolism because less than 1% of thiopental is recovered unchanged in urine.²¹⁴ The time required for the plasma concentration of thiopental to decrease 50% after discontinuation of a prolonged infusion (context-sensitive half-time) is lengthy. The drug is sequestered in fat and skeletal muscle and then it reenters the circulation and prevents the plasma concentration from dropping rapidly.¹⁹

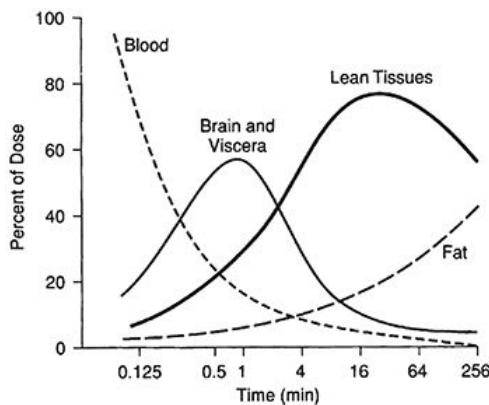


FIGURE 5.19 After a rapid intravenous injection, the percentage of thiopental remaining in the blood rapidly decreases as drug moves from the blood to tissues. Time to achievement of peak levels is a direct function of tissue capacity for barbiturate relative to blood flow. Initially, most thiopental is taken up by the vessel-rich group tissues because of their high blood flow. Subsequently, drug is redistributed to skeletal muscles and, to a lesser extent, to fat. The rate of metabolism equals the early rate of removal by fat, and the sum of these two events is similar to uptake of drug by skeletal muscles. *Reprinted with permission from Saidman LJ. Uptake, distribution, and elimination of barbiturates. In: Eger EI, ed. Anesthetic Uptake and Action. Baltimore, MD: Williams & Wilkins; 1974.*

Thiobarbiturates are metabolized in hepatocytes and, to a small extent, in extrahepatic sites such as the kidneys and possibly the CNS. Metabolites (particularly hydroxythiopental and the 5-carboxylic acid) are usually inactive and are always more water soluble than the parent compound, which facilitates renal excretion. Ultimately, metabolism of thiopental is almost complete (99%). Hepatic clearance of thiopental is characterized by a low hepatic extraction ratio and capacity-dependent elimination. This means factors affecting hepatic enzyme activity should change clearance. However, the reserve capacity of the liver to oxidize barbiturates is huge, so hepatic dysfunction must be extreme before a prolonged duration of action occurs.

In pediatric patients, the elimination half-time of thiopental is shorter than in adults.²¹⁵ This is due to more rapid hepatic clearance of thiopental by pediatric patients. Therefore, recovery after large or repeated doses of thiopental may be more rapid for infants and children than for adults. Protein binding and V_d of thiopental are not different in pediatric and adult patients. Elimination half-time is prolonged during pregnancy because of the increased protein binding of thiopental.

Pharmacodynamics and Clinical Applications

Premedication

Oral and injectable barbiturates have been replaced by benzodiazepines for preanesthetic medication. Drowsiness may last for only a short time after a sedative-hypnotic dose of a barbiturate is administered orally, but residual CNS effects characterized as “hangover” may persist. The rapid onset of action of barbiturates renders these drugs useful for treatment of grand mal seizures, but, again, benzodiazepines are probably superior, providing a more specific site of action in the CNS. Rectal administration of barbiturates, especially methohexitol, 20 to 30 mg/kg, has been used to induce anesthesia in uncooperative or young

patients.²¹⁶ Loss of consciousness after rectal administration of methohexitol correlates with a plasma concentration greater than 2 µg/mL.²¹⁷

Induction of Anesthesia

The relative potency of barbiturates used for IV induction of anesthesia assumes that thiopental is 1, thiamylal is 1.1, and methohexitol is 2.5. At a blood pH of 7.4, methohexitol is 76% nonionized compared with 61% for thiopental, which is consistent with the greater potency of methohexitol. These drugs produce minimal to no direct effects on skeletal, cardiac, or smooth muscles. Induction dose requirements for thiopental vary with patient age, weight, and most importantly cardiac output. The dose of thiopental required to induce anesthesia decreases with age, reflecting a slower passage of barbiturate from the central compartment to peripheral compartments (Figure 5.20).^{218,219} The dose of thiopental needed to produce anesthesia in early pregnancy (7–13 weeks of gestation) is decreased about 18% compared with that for nonpregnant females (Figure 5.21).²²⁰ Thiopental requirements, for unknown reasons, seem to be increased in children for more than 1 year after thermal injury.²²¹ Despite a contrary clinical impression, thiopental dose requirements (with EEG suppression as the end point) are not different between nonalcoholics and alcoholics with abstinence of 9 to 17 days and 30 days (Figure 5.22).²²²

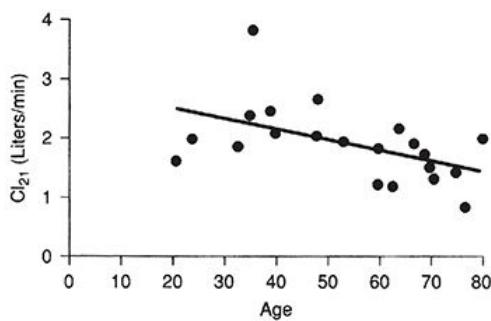


FIGURE 5.20 The rate of intercompartmental clearance of thiopental from the central compartment to the peripheral compartment slows with increasing age. Reprinted with permission from Avram JJ, Krejcie TC, Henthorn TK. The relationship of age to the pharmacokinetics to early drug distribution: the concurrent disposition of thiopental and indocyanine green. *Anesthesiology*. 1990;72(3):403-411. Copyright © 1990 American Society of Anesthesiologists, Inc.

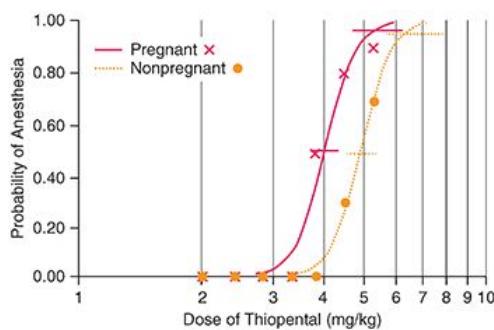


FIGURE 5.21 Dose-response curves for anesthesia in pregnant and nonpregnant females demonstrate a decreased dose requirement during 7 to 13 weeks of gestation. Reprinted with permission from Gin T, Mainland P, Chan MT, et al. Decreased thiopental requirements in early pregnancy. *Anesthesiology*. 1997;86(1):73-78. Copyright © 1997 American Society of Anesthesiologists, Inc.

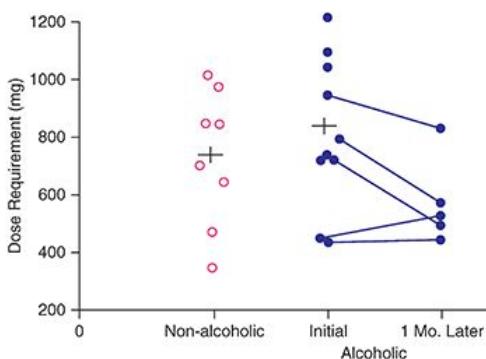


FIGURE 5.22 Thiopental doses needed to achieve burst suppression with 3 seconds of an isoelectric electroencephalogram are similar in nonalcoholic and alcoholic patients with abstinence of 9 to 17 days (initial) and 30 days (1 month later). Reprinted with permission from Swerdlow BN, Holley FO, Maitre PO, et al. Chronic alcohol intake does not change thiopental anesthetic requirements, pharmacokinetics, or pharmacodynamics. Anesthesiology. 1990;72(3):455-461. Copyright © 1990 American Society of Anesthesiologists, Inc.

Methohexitol is the only barbiturate with pharmacodynamic effects sufficiently different from thiopental and thiamylal to offer an alternative for IV induction. One advantage of methohexitol is its effect to lower the seizure threshold. Methohexitol, but not thiopental, is effective in inducing seizure activity in patients with psychomotor epilepsy undergoing temporal lobe resection of seizure-producing areas.^{223,224} The decreased anticonvulsant effect of methohexitol is useful during electroconvulsive therapy because the therapeutic effect is related to the duration of the seizure. The principal disadvantage of methohexitol is the incidence of excitatory phenomena, such as involuntary skeletal muscle movements (myoclonus) and other signs of excitatory activity including hiccoughs. These phenomena are dose dependent and may be decreased by pretreatment with opioids.

Even before the removal of barbiturates from the US market, propofol had replaced them for induction of anesthesia in most cases. The time to awaken from a single induction dose of propofol was not that different, but it produced less nausea, and generally, patients met recovery milestones (voiding, walking) more rapidly, especially in those where rapid awakening is considered desirable.

Treatment of Increased Intracranial Pressure and Ischemic Injury

Barbiturates can be administered to decrease refractory ICP that remains increased despite other measures. Barbiturates decrease ICP by decreasing cerebral blood volume through drug-induced cerebral vascular vasoconstriction and an associated decrease in cerebral blood flow. The decrease in cerebral blood flow and increase in the perfusion-to-metabolism ratio made thiopental a useful drug for induction of anesthesia in patients with increased ICP ([Figure 5.23](#)).²²⁵ The drug can be titrated to a level that produces EEG burst suppression, and an isoelectric EEG occurs with maximal (~55%) barbiturate-induced depression of CMRO₂. However, this therapy produces significant hypotension, and improved outcome after head trauma has not been demonstrated in patients treated with barbiturates, despite the ability of these drugs to decrease and control ICP.²²⁶

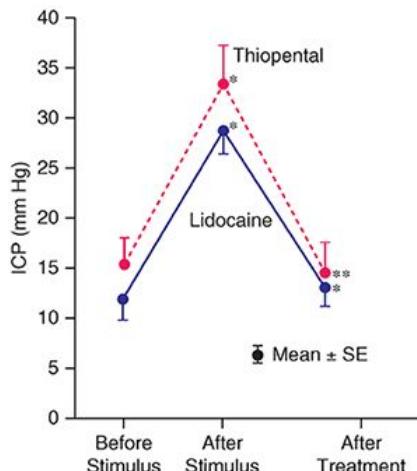


FIGURE 5.23 The administration of thiopental, 3 mg/kg intravenously (IV), is as effective as lidocaine, 1.5 mg/kg IV, in decreasing intracranial pressure (ICP) after surgical stimulation in patients with brain tumors. * $P < .025$ versus preceding value; ** $P < .02$ versus preceding value. Reprinted with permission from Bedford RF, Persing JA, Pobereskin L, et al. Lidocaine or thiopental for rapid control of intracranial hypertension? Anesth Analg. 1980;59(6):435-437. Copyright © 1980 International Anesthesia Research Society.

Barbiturate therapy has also been used to improve brain survival after global cerebral ischemia due to cardiac arrest, but the efficacy for this indication remains unproven.²²⁷ There are data suggesting that neuropsychiatric complications after cardiopulmonary bypass (presumably due to embolism) clear more rapidly in patients treated prospectively with thiopental to maintain an isoelectric EEG.²²⁸ There is insufficient evidence, however, to support routine use of this therapy.

In contrast to global cerebral ischemia, animal studies consistently show improved outcome with barbiturate therapy of incomplete (focal) cerebral ischemia that permits drug-induced metabolic suppression.²²⁹ In this regard, barbiturate-induced decreases in CMRO₂ exceed decreases in cerebral blood flow, which may provide protection to poorly perfused areas of the brain. The routine use of barbiturates during cardiac surgery or after stroke is not recommended because moderate degrees of hypothermia (33°C–34°C) appear to provide superior neuroprotection without prolonging the recovery phase.

Side Effects

Side effects, especially on the cardiovascular system, inevitably accompany the clinical use of barbiturates. In normovolemic subjects, thiopental, 5 mg/kg IV, produces a transient 10- to 20-mm Hg decrease in blood pressure that is offset by a compensatory 15 to 20 beats per minute increase in heart rate (Figure 5.24).²³⁰ The mild and transient decrease in systemic blood pressure that accompanies induction of anesthesia with barbiturates is principally due to peripheral vasodilation, reflecting depression of the medullary vasomotor center and decreased sympathetic nervous system outflow from the CNS. This dose of thiopental produces minimal to no evidence of direct myocardial depression.

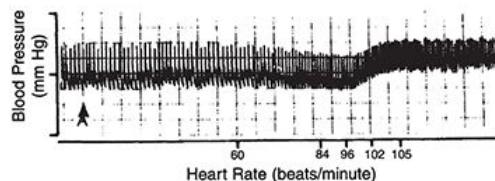


FIGURE 5.24 In normovolemic patients, the rapid administration of thiopental, 5 mg/kg IV (A), is followed by a modest decrease in blood pressure, which is subsequently offset by a compensatory increase in heart rate. Reprinted with permission from Filner BF, Karliner JS. Alterations of normal left ventricular

performance by general anesthesia. Anesthesiology. 1976;45(6):610-621. Copyright © 1976 American Society of Anesthesiologists, Inc.

Ventilation

Barbiturates also produce dose-dependent depression of medullary and pontine ventilatory centers. Thiopental decreases the sensitivity of the medullary ventilatory center to stimulation of carbon dioxide, and apnea is especially likely in the presence of other depressant drugs. Resumption of spontaneous ventilation after a single IV induction dose of barbiturate is characterized by a slow frequency of breathing and decreased tidal volume. Laryngeal reflexes and the cough reflex are not depressed until large doses of barbiturates have been administered.

Somatosensory Evoked Responses

Thiopental produces dose-dependent changes in median nerve somatosensory evoked responses and brainstem auditory evoked responses. However, some response is always obtainable,²³¹ so thiopental is an acceptable drug to administer when the ability to monitor somatosensory evoked potentials is desirable.

Other Effects

Enzyme Induction

Barbiturates, especially phenobarbital, stimulate an increase in liver microsomal protein content (enzyme induction) after 2 to 7 days of sustained drug administration. Altered drug responses and drug interactions may reflect barbiturate-induced enzyme induction, resulting in accelerated metabolism of (1) other drugs, such as oral anticoagulants, phenytoin, and tricyclic antidepressants, or (2) endogenous substances, including corticosteroids, bile salts, and vitamin K. The production of heme is accelerated, and this may exacerbate acute intermittent porphyria in susceptible patients.

Intra-arterial Injection

Inadvertent intra-arterial injection of thiopental usually results in immediate, intense vasoconstriction and excruciating pain that radiates along the distribution of the artery. Vasoconstriction may obscure distal arterial pulses and blanching of the extremity is followed by cyanosis. Gangrene and permanent nerve damage may occur. Treatment of accidental intra-arterial injection of a barbiturate includes immediate attempts to dilute the drug, prevention of arterial spasm by injecting vasodilators such as lidocaine or papaverine, and general measures to sustain adequate blood flow.

Allergic Reactions

Allergic reactions in association with IV administration of barbiturates for induction of anesthesia most likely represent anaphylaxis (antigen–antibody interaction). Nevertheless, thiopental can also produce signs of an allergic reaction in the absence of prior exposure, suggesting an anaphylactoid response.²³² Although true anaphylaxis can occur, some of these reactions appear to be anaphylactoid responses due to direct release of histamine from tissue mast cells.^{232–234} The incidence of allergic reactions to thiopental is estimated to be 1 per 30,000 patients.²³⁵ The majority of reported cases are in patients with a history of chronic atopy who often have received thiopental previously without adverse responses.

Non- γ -Aminobutyric Acid Sedatives and Hypnotics

Ketamine

Ketamine is a phencyclidine derivative that produces “dissociative anesthesia,” which is characterized by evidence on the EEG of dissociation between the thalamocortical and limbic systems.^{236,237} Dissociative anesthesia resembles a cataleptic state in which the eyes remain open with a slow nystagmic gaze. The patient is noncommunicative, although wakefulness may appear to be present. Varying degrees of hypertonus and purposeful skeletal muscle movements often occur independently of surgical stimulation. The patient is

amnesia, and analgesia is intense. Ketamine has advantages over propofol and etomidate in not requiring a lipid emulsion vehicle for dissolution and in producing profound analgesia at subanesthetic doses. However, the frequency of emergence delirium limits the clinical usefulness of ketamine as a sole agent. Ketamine is a drug with significant abuse potential, emphasizing the need to take appropriate precautions against unauthorized nonmedical use.

Structure–Activity Relationships

Ketamine is a water-soluble molecule that structurally resembles phencyclidine. The presence of an asymmetric carbon atom results in the existence of two optical isomers of ketamine.²³⁶ The left-handed optical isomer of ketamine is designated S(+) ketamine (esketamine), and the right-handed optical isomer is designated R(–) ketamine. In the United States, the racemic form of ketamine has been the most frequently used preparation, although esketamine is clinically available for treatment of therapy-resistant depression (Spravato). In Europe, esketamine is widely used as anesthetic and in the treatment of acute and chronic pain. When studied separately, esketamine produces (1) more intense analgesia, (2) more rapid metabolism and thus recovery, (3) less salivation, and (4) a lower incidence of emergence reactions than R(–) ketamine.^{238,239} For example, the analgesic potency of esketamine is approximately twice that of racemic ketamine and 4 times greater than R(–) ketamine. Ketamine isomer induces less fatigue and cognitive impairment than equianalgesic small-dose racemic ketamine.²⁴⁰ Both isomers of ketamine appear to inhibit uptake of catecholamines back into postganglionic sympathetic nerve endings (cocaine-like effect). The fact that individual optical isomers of ketamine differ in their pharmacologic properties suggests that this drug interacts with specific receptors to induce these behaviors. The preservative used for ketamine is benzethonium chloride, but also preservative-free ketamine is available.

Mechanism of Action

The mechanism of action of ketamine-induced analgesia and dissociative anesthesia is unknown. Ketamine is known to interact with multiple CNS receptors, but clear association between receptor interaction and specific behavior has not been established. Ketamine binds noncompetitively to the phencyclidine recognition site on N-methyl-D-aspartate (NMDA) receptors. In addition, ketamine exerts effects at other sites including opioid receptors, monoaminergic receptors, muscarinic receptors, and voltage-sensitive sodium and L-type calcium channels and neuronal nicotinic acetylcholine receptors.^{241–243} Unlike propofol and etomidate, ketamine has only weak actions at GABA_A receptors. Inflammatory mediators produced locally by compression of nerve roots can activate neutrophils that then adhere to blood vessels and impair blood flow. Ketamine suppresses neutrophil production of inflammatory mediators and improves blood flow.²⁴⁴ Direct inhibition of cytokines in blood by ketamine may contribute to the analgesic effects of this drug. In neuropathic pain, ketamine's antiinflammatory and analgesic effects appear to be mediated by the innate repair receptor (CD131-erythropoietin receptor complex).²⁴⁵ This receptor plays a pivotal role in subduing tissue damage and inflammation. Activation of the receptor system by ketamine effectively relieves neuropathic pain from peripheral nerve injury, which is not observed in mice lacking the CD131 receptor.²⁴⁵ Ketamine-induced relief of acute pain is not affected by the innate repair receptor because acute pain relief was maintained in mice without the CD131 receptor.

N-Methyl-D-Aspartate Receptor Antagonism

The NMDA receptors (members of the glutamate receptors family) are ligand-gated ion channels that are unique in that channel activation requires binding of the excitatory neurotransmitter, glutamate with glycine as an obligatory coagonist ([Figure 5.25](#)).²³⁶ Ketamine inhibits activation of NMDA receptors by glutamate and decreases presynaptic release of glutamate. The interaction with phencyclidine binding sites appears to be stereoselective, with the S(+) isomer of ketamine having the greatest affinity.

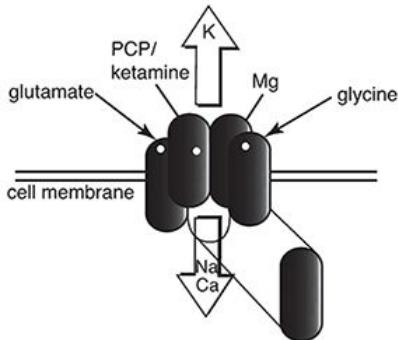


FIGURE 5.25 Schematic diagram of the *N*-methyl-D-aspartate (NMDA) glutamate receptor channel complex. The receptor consists of five subunits surrounding a central ion channel that is permeable to calcium, potassium, and sodium. Binding sites for the agonist glutamate and the obligatory coagonist glycine are indicated. The NMDA receptors are ligand-gated ion channels that are activated by the excitatory neurotransmitter glutamate. Glutamate is the most abundant neurotransmitter in the central nervous system. One of the subunits has been removed to show the interior of the ion channel and binding sites for magnesium and ketamine, which produce noncompetitive NMDA receptor blockade. *Reprinted with permission from Kohrs R, Durieux ME. Ketamine: teaching an old drug new tricks. Anesth Analg.* 1998;87(5):1186-1193. Copyright © 1998 International Anesthesia Research Society.

Opioid Receptors

Ketamine has been reported to directly interact with μ -, δ -, and α -opioid receptors.²⁴⁶ In contrast, other studies have suggested ketamine may be an antagonist at μ receptors and an agonist at α receptors. Ketamine also weakly interacts with δ receptors.

Monoaminergic Receptors

The antinociceptive action of ketamine may involve activation of descending inhibitory monoaminergic pain pathways.

Muscarinic Receptors

Ketamine anesthesia is partially antagonized by anticholinesterase drugs. The fact that ketamine produces anticholinergic symptoms (emergence delirium, bronchodilation, sympathomimetic action) suggests that an antagonist effect of ketamine at muscarinic receptors is more likely than an agonist effect.

Sodium Channels

Consistent with its mild local anesthetic-like properties, ketamine interacts with voltage-gated sodium channels, sharing a binding site with local anesthetics.²⁴²

Neuronal Nicotinic Acetylcholine Receptors

Ketamine interacts with both heteromeric and homomeric α_7 nicotinic acetylcholine receptors.²⁴³ In α_7 -type nicotinic receptors, a single subunit has been identified as a binding site in the extracellular loop between transmembrane segments 2 and 3.²⁴⁷ Nicotinic inhibition by ketamine does not appear to affect sedation or immobility but may play a role in its analgesic effects.²⁴⁸

Pharmacokinetics

The pharmacokinetics of ketamine are similar to thiopental in rapid onset of action, relatively short duration of action, and high lipid solubility (see [Table 5.1](#)). Ketamine has a pK of 7.5 at physiologic pH. Peak plasma concentrations of ketamine occur within 1 minute after IV administration and within 5 minutes after IM injection. Ketamine is not significantly bound to plasma proteins and leaves the blood rapidly to be

distributed into tissues. Initially, ketamine is distributed to highly perfused tissues such as the brain, where the peak concentration may be 4 or 5 times that present in plasma. The extreme lipid solubility of ketamine (5–10 times that of thiopental) ensures its rapid transfer across the blood–brain barrier. Furthermore, ketamine-induced increases in cerebral blood flow could facilitate delivery of drug and thus enhance rapid achievement of high brain concentrations. Subsequently, ketamine is redistributed from the brain and other highly perfused tissues to less well-perfused tissues, the release of which results in late psychodynamic effects after emergence. Ketamine has a high hepatic clearance rate (1 L per minute) and a large V_d (3 L/kg), resulting in an elimination half-time of 2 to 3 hours. The high hepatic extraction ratio suggests that alterations in hepatic blood flow could influence ketamine’s clearance rate.

Metabolism

Ketamine is metabolized extensively by hepatic microsomal enzymes. An important pathway of metabolism is demethylation of ketamine by cytochrome P450 enzymes to form norketamine and subsequently hydroxynorketamine (**Figure 5.26**).²⁴⁹ In animals, norketamine is one-fifth to one-third as potent as ketamine. This active metabolite may contribute to prolonged effects of ketamine (analgesia), especially with repeated doses or a continuous IV infusion. After IV administration, less than 4% of a dose of ketamine can be recovered from urine as unchanged drug. Fecal excretion accounts for less than 5% of an injected dose of ketamine. Chronic administration of ketamine stimulates the activity of enzymes responsible for its metabolism. Accelerated metabolism of ketamine as a result of enzyme induction could explain, in part, the observation of tolerance to the analgesic effects of ketamine that occurs in patients receiving repeated doses of this drug. Indeed, tolerance may occur in burn patients receiving more than two short-interval exposures to ketamine.²⁵⁰ Development of tolerance is also consistent with reports of ketamine dependence.²⁴⁹

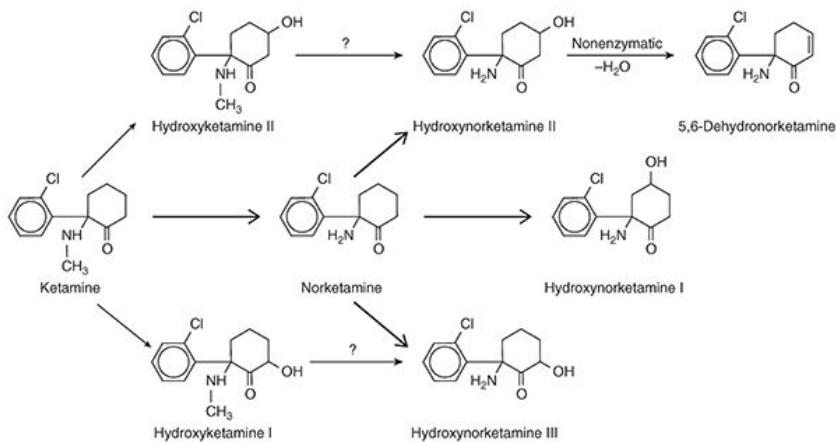


FIGURE 5.26 Metabolism of ketamine. Reprinted with permission from White PF, Way WL, Trevor AJ. *Ketamine – its pharmacology and therapeutic uses*. Anesthesiology. 1982;56(2):119-136. Copyright © 1982 American Society of Anesthesiologists, Inc.

Clinical Uses

Ketamine is a unique drug evoking intense analgesia at subanesthetic doses and producing prompt induction of anesthesia when administered IV at higher doses. Inclusion of an antiallalogue in the preoperative medication is often recommended to decrease the likelihood of coughing and laryngospasm due to ketamine-induced salivary secretions. Glycopyrrolate may be preferable, as atropine or scopolamine can easily cross the blood–brain barrier and could theoretically increase the incidence of emergence delirium (see “[Emergence Delirium \[Psychedelic Effects\]](#)” section).

Analgesia

Intense analgesia can be achieved with subanesthetic doses of ketamine, 0.2 to 0.5 mg/kg IV.²⁵¹ Plasma concentrations of ketamine that produce analgesia are lower after oral than IM administration, presumably reflecting a higher norketamine concentration due to hepatic first-pass metabolism that occurs after oral administration. Analgesia is thought to be greater for somatic than for visceral pain. The analgesic effects of ketamine are likely due to its activity in the thalamic and limbic systems, which are responsible for the interpretation of painful signals. Additionally, ketamine activates descending inhibition.²⁵² Small doses of ketamine are also useful adjuvants to opioid analgesia.²⁵³

Spinal cord sensitization is responsible for pain associated with touching or moving an injured body part that would normally not be painful (allodynia). Central to the development of spinal cord sensitization is activation of NMDA receptors, which are located in the spinal cord dorsal horn. The NMDA receptors are excitatory amino acid receptors that are important in pain processing and the modulation of pain.²⁵⁴ Excitatory amino acids, particularly glutamate, acting at NMDA receptors play an important role in spinal nociceptive pathways. Inhibition of spinal NMDA receptors by drugs, such as ketamine, magnesium, and dextromethorphan, is useful in the management of postoperative pain including decreases in analgesic consumption. Analgesia can be produced during labor without associated depression of the neonate.^{255 256} Neonatal neurobehavioral scores of infants born by vaginal delivery with ketamine analgesia are lower than those for infants born with epidural anesthesia but higher than the scores in infants delivered with thiopental–nitrous oxide anesthesia.²⁵⁷ Postoperative sedation and analgesia after pediatric cardiac surgery can be produced by continuous infusions of ketamine, 1 to 2 mg/kg/hour. Ketamine is useful as an analgesic adjuvant in patients with preexisting chronic pain syndromes who require surgery.

Ketamine metabolites may play a role in the production of analgesia. In three rodent pain models (nerve-injury neuropathic pain, tibia fracture complex regional pain syndrome pain, and plantar incision postoperative pain), it was shown that hydroxynorketamine produces long-lasting pain relief (outlasting the effects of ketamine) without causing motor incoordination.²⁵⁸ Moreover, hydroxynorketamine has a lower potential for abuse or addiction and is associated with profound antidepressant effects.

Neuraxial Analgesia

The efficacy of extradural ketamine is controversial. Although ketamine has been reported to interact with opioid receptors, the affinity for spinal opioid receptors may be 10,000-fold weaker than that of morphine.²⁵⁹ It seems likely that extradural effects of ketamine (30 mg) are due to both spinal and systemic effects and possibly interaction with local anesthetic binding sites on voltage-gated sodium ion channels. Overall, the epidural effects of ketamine are relatively small, but in combination with other epidural analgesics (opioids, local anesthetics), an additive or synergistic effect may occur.²⁶⁰ Intrathecal administration of ketamine (5-50 mg in 3 mL of saline) produces variable and brief analgesia, unless the ketamine is also combined with epinephrine to slow systemic absorption. The neuraxial use of ketamine to produce analgesia appears to be of limited value and is not an approved indication.²⁴¹

Induction of Anesthesia

Induction of anesthesia is produced by administration of ketamine, 1 to 2 mg/kg IV or 4 to 8 mg/kg IM. Injection of ketamine IV does not produce pain or venous irritation. The need for large IV doses reflects a significant first-pass hepatic effect for ketamine. Consciousness is lost in 30 to 60 seconds after IV administration and in 2 to 4 minutes after IM injection. Unconsciousness is associated with maintenance of normal or only slightly depressed pharyngeal and laryngeal reflexes. Return of consciousness usually occurs in 10 to 20 minutes after an injected induction dose of ketamine but return to full orientation may require an additional 60 to 90 minutes. Emergence times are even longer after repeated IV injections or a continuous infusion of ketamine. Amnesia persists for about 60 to 90 minutes after recovery of consciousness, but ketamine does not produce retrograde amnesia. Because of its rapid onset of action, ketamine has been used as an IM induction drug in children and difficult-to-manage mentally challenged patients regardless of age. Due to its intense analgesic activity, ketamine has been used extensively for burn dressing changes, debridement, and skin grafting procedures. The excellent analgesia and ability to maintain spontaneous

ventilation in an airway that might otherwise be altered by burn scar contractures are important advantages of ketamine in these patients. Tolerance may develop, however, in burn patients receiving repeated, short-interval anesthesia with ketamine.^{[250](#)}

Induction of anesthesia in acutely hypovolemic patients is often accomplished with ketamine, taking advantage of the drug's cardiovascular-stimulating effects. In this regard, it is important to recognize that ketamine, like all injected anesthetics, may become a myocardial depressant if endogenous catecholamine stores are depleted and sympathetic nervous system compensatory responses are impaired.^{[261](#)}

The administration of ketamine to patients with coronary artery disease is complicated by increased myocardial oxygen requirements that may accompany this drug's sympathomimetic effects on the heart. Furthermore, the absence of cardioprotective effects (preconditioning) associated with racemic ketamine is a consideration when this drug is administered to patients with known coronary artery disease (see the "[Drug Interactions](#)" section on preconditioning). Nevertheless, induction of anesthesia with administration of diazepam, 0.5 mg/kg IV, and ketamine, 0.5 mg/kg IV, followed by a continuous infusion of ketamine, 15 to 30 µg/kg/minute IV, has been used for anesthesia in patients with coronary artery disease historically.^{[249](#)} The combination of subanesthetic doses of ketamine with propofol for production of total IV anesthesia has been reported to produce more stable hemodynamics than propofol and fentanyl while avoiding the undesirable emergence reactions that may accompany administration of higher doses of ketamine.^{[262](#)}

The beneficial effects of ketamine on airway resistance due to drug-induced bronchodilation make this a potentially useful drug for rapid IV induction of anesthesia in patients with asthma.^{[263](#)}

Ketamine should be used cautiously or avoided in patients with systemic or pulmonary hypertension or increased ICP, although this recommendation may deserve reevaluation based on more recent data (see the "[Central Nervous System](#)" and "[Cardiovascular System](#)" sections). Nystagmus associated with administration of ketamine may be undesirable in operations or examinations of the eye performed under anesthesia.

Ketamine has been administered safely to patients with malignant hyperthermia and does not trigger the syndrome in susceptible swine.^{[264](#)} Extensive experience with ketamine for pediatric cardiac catheterization has shown the drug to be useful, but its possible cardiac-stimulating effects must be considered in the interpretation of catheterization data.

Reversal of Opioid Tolerance

Subanesthetic doses of ketamine are effective in preventing and reversing morphine-induced tolerance.^{[265](#)} Although the mechanism of opioid-induced tolerance is unknown, it is believed to involve interaction between NMDA receptors, the nitric oxide pathway, and µ-opioid receptors. Administration of subanesthetic doses of ketamine (0.3 mg/kg/hour) reduces the likelihood of opioid tolerance and improves analgesia.

Improvement of Psychiatric Disorders

The NMDA receptors for glutamate are thought to be involved in the pathophysiology of mental depression and the mechanism of action of antidepressants. Ketamine in small doses improved the postoperative depressive state in patients with mental depression.^{[266](#)} Intermittent treatment with low-dose ketamine also results in long-term suppression of obsessions and compulsions in patients with obsessive-compulsive disorder.^{[267](#)} Recently, the FDA-approved intranasal esketamine in conjunction with an oral antidepressant for treatment of therapy-resistant depression (Spravato).

Restless Leg Syndrome

A single case report describes symptomatic improvement in two patients with restless leg syndrome treated with oral ketamine.^{[268](#)} It is possible that ketamine inhibits neuroinflammation in the spinal cord or higher centers. Within the spinal cord, restless leg syndrome may reflect NMDA receptor activation and production of inflammatory mediators that impair spinal cord blood flow.

Side Effects

Ketamine is unique among injected anesthetics in its ability to stimulate the cardiovascular system and produce emergence delirium.²³⁷ Although generally considered contraindicated in patients with increased ICP, it must be recognized that many of the early studies of ketamine's effects on ICP were conducted on spontaneously breathing subjects.²³⁷

Central Nervous System

Ketamine is traditionally considered to increase cerebral blood flow and CMRO₂, although there is also evidence suggesting that this may not be a valid generalization.²³⁷

Intracranial Pressure

Ketamine is reported to be a potent cerebral vasodilator capable of increasing cerebral blood flow by 60% in the presence of normocapnia.²⁶⁹ As a result, patients with intracranial pathology are commonly considered vulnerable to sustained increases in ICP after administration of ketamine. Nevertheless, in mechanically ventilated animals with increased ICP, there was no further increase in ICP after administration of ketamine, 0.5 to 2.0 mg/kg IV.²⁷⁰ Furthermore, anterior fontanelle pressure, an indirect monitor of ICP, decreases in mechanically ventilated preterm neonates after administration of ketamine, 2 mg/kg IV.²⁷¹ In patients requiring craniotomy for brain tumor or cerebral aneurysm resection, administration of ketamine, 1 mg/kg IV, did not increase middle cerebral artery blood flow velocity, and ICP decreased modestly (**Figure 5.27**).²⁷² In patients with traumatic brain injury, the administration of ketamine, 1.5, 3.0, and 5.0 mg/kg IV, during mechanical ventilation of the lungs resulted in significant decreases in ICP regardless of the dose of ketamine.²⁷³ These results in patients suggest that ketamine can be administered to patients with mildly increased ICP if administered with mild hyperventilation without adversely altering cerebral hemodynamics. Prior administration of thiopental, diazepam, or midazolam has been shown to blunt ketamine-induced increases in cerebral blood flow.

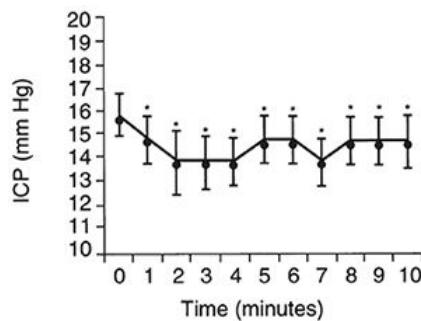


FIGURE 5.27 In patients with a brain tumor or cerebral aneurysm, the administration of ketamine, 1 mg/kg intravenously, during mechanical ventilation of the lungs with nitrous oxide and isoflurane was associated with a modest decrease in intracranial pressure (ICP). This decrease in ICP was accompanied by a corresponding decrease in cerebral artery blood flow velocity. Reprinted with permission from Mayberg TS, Lam AM, Matta BF, et al. Ketamine does not increase cerebral blood flow velocity or intracranial pressure during isoflurane/nitrous oxide anesthesia in patients undergoing craniotomy. Anesth Analg. 1995;81(1):84-89. Copyright © 1995 International Anesthesia Research Society.

Neuroprotective Effects

Activation of NMDA receptors has been implicated in cerebral ischemic damage.²⁴¹ The antagonist effect of ketamine on NMDA receptors suggests a possible neuroprotective role for this drug although this remains an unproved hypothesis. Indeed, S(+) ketamine offers no greater neuroprotection than remifentanil.²⁷⁴

Electroencephalogram

Ketamine's effects on the EEG are characterized by abolition of alpha rhythm and dominance of θ activity. Onset of δ activity coincides with loss of consciousness. At high doses, ketamine produces a burst suppression pattern. Ketamine-induced excitatory activity occurs in both the thalamus and limbic systems without evidence of subsequent spread of seizure activity to cortical areas.²⁷⁵ As such, ketamine would be unlikely to precipitate generalized convulsions in patients with seizure disorders. Indeed, ketamine does not alter the seizure threshold in epileptic patients.²⁷⁶ Although myoclonic- and seizure-like activity may occur in normal patients, EEG evidence of cortical epileptic activity is absent and ketamine is considered to possess anticonvulsant activity.²⁷⁷

Somatosensory Evoked Potentials

Ketamine increases the cortical amplitude of somatosensory evoked potentials.²⁷⁸ This ketamine-induced increase in amplitude is attenuated by nitrous oxide. Auditory and visual evoked responses are decreased by ketamine.

Cardiovascular System

Ketamine produces cardiovascular effects that resemble sympathetic nervous system stimulation. Indeed, a direct negative cardiac inotropic effect is usually overshadowed by central sympathetic stimulation.

Hemodynamic Effects

Systemic and pulmonary arterial blood pressure, heart rate, cardiac output, cardiac work, and myocardial oxygen requirements are increased after IV administration of ketamine (**Table 5.4**).²⁷⁹ The increase in systolic blood pressure in adults receiving clinical doses of ketamine is 20 to 40 mm Hg, with a slightly smaller increase in diastolic blood pressure. Typically, systemic blood pressure increases progressively during the first 3 to 5 minutes after IV injection of ketamine and then decreases to predrug levels over the next 10 to 20 minutes. The cardiovascular-stimulating effects on the systemic and pulmonary circulations are blunted or prevented by prior administration of benzodiazepines or concomitant administration of inhaled anesthetics, including nitrous oxide.^{237,280} Likewise, ketamine administered to mildly sedated infants fails to produce hemodynamic changes in either the systemic or pulmonary circulation.²⁸¹

TABLE 5.4

Circulatory effects of ketamine

	Control	Ketamine (2 mg/kg IV)	% Change
Heart rate (beats per minute)	74	98	+33
Mean arterial pressure (mm Hg)	93	119	+28
Stroke volume index (mL/m ²)	43	44	
Systemic vascular resistance (units)	16.2	15.9	
Right atrial pressure (mm Hg)	7.0	8.9	
Left ventricular end-diastolic pressure (mm Hg)	13.0	13.1	
Pulmonary artery pressure (mm Hg)	17.0	24.5	+44
Minute work index (kg/minute/m ²)	5.4	8.9	+40
Tension-time index (mm Hg per second)	2,700	4,600	+68

Critically ill patients occasionally respond to ketamine with unexpected decreases in systemic blood pressure and cardiac output, which reflect depletion of endogenous catecholamine stores and exhaustion of sympathetic nervous system compensatory mechanisms, leading to an unmasking of ketamine's direct myocardial depressant effects.^{261,282} Conversely, ketamine has been shown to decrease the need for inotropic support in septic patients, perhaps reflecting an inhibition of catecholamine reuptake.^{283,284}

In shocked animals, ketamine is associated with an increased survival rate compared with animals anesthetized with halothane.²⁸⁵ Blood pressure may be better maintained in hemorrhaged animals

anesthetized with ketamine. However, ketamine administration is associated with greater increases in arterial lactate concentrations than occur in animals with lower systemic blood pressures anesthetized with a volatile anesthetic.²⁸⁶ This suggests inadequate tissue perfusion despite maintenance of systemic blood pressure by ketamine. Presumably, ketamine-induced vasoconstriction maintains systemic blood pressure at the expense of tissue perfusion.

Cardiac Rhythm

The effect of ketamine on cardiac rhythm is inconclusive. There is evidence that ketamine enhances the dysrhythmogenicity of epinephrine.²⁸⁷ Conversely, ketamine may abolish epinephrine-induced cardiac dysrhythmias.

Mechanisms of Cardiovascular Effects

The mechanisms for ketamine-induced cardiovascular effects are complex. Direct stimulation of the CNS leading to increased sympathetic nervous system outflow seems to be the most important mechanism for cardiovascular stimulation.²⁸⁸ Evidence for this mechanism is the ability of inhaled anesthetics, ganglionic blockade, β -blockade, cervical epidural anesthesia, and spinal cord transection to prevent ketamine-induced increases in systemic blood pressure and heart rate.^{289,290} Furthermore, increases in plasma concentrations of epinephrine and norepinephrine occur as early as 2 minutes after IV administration of ketamine and return to control levels 15 minutes later.²⁹¹ In vitro, ketamine produces direct myocardial depression, emphasizing the importance of an intact sympathetic nervous system for the cardiac-stimulating effects of this drug.²⁹² The role of ketamine-induced inhibition of norepinephrine uptake (reuptake) into postganglionic sympathetic nerve endings and associated increases of plasma catecholamine concentrations on the drug's cardiac-stimulating effects are not known.²⁸⁷

Ventilation and Airway

Ketamine does not produce significant depression of ventilation. The ventilatory response to carbon dioxide is maintained during ketamine anesthesia, and the PaCO_2 is unlikely to increase more than 3 mm Hg.²⁹³

Breathing frequency typically decreases for 2 to 3 minutes after administration of ketamine. Apnea, however, can occur if the drug is administered rapidly IV or an opioid is included in the preoperative medication.

Upper airway skeletal muscle tone is well maintained, and upper airway reflexes remain relatively intact after administration of ketamine.²⁹⁴ Despite continued presence of upper airway reflexes, ketamine anesthesia does not negate the need for protection of the lungs against aspiration by placement of a cuffed tube in the patient's trachea. Salivary and tracheobronchial mucous gland secretions are increased by IM or IV administration of ketamine, leading to the frequent recommendation that an antisialagogue be included in the preoperative medication when use of this drug is anticipated.

Bronchomotor Tone

Ketamine has bronchodilatory activity and is as effective as halothane or enflurane in preventing experimentally induced bronchospasm in dogs.²⁶³ Ketamine has been used in subanesthetic doses to treat bronchospasm in the operating room and ICU. Successful treatment of status asthmaticus with ketamine has been reported.²⁹⁵ In the presence of active bronchospasm, ketamine may be recommended as the IV induction drug of choice. The mechanism by which ketamine produces airway relaxation is unclear, although several mechanisms have been suggested, including increased circulating catecholamine concentrations, inhibition of catecholamine uptake, voltage-sensitive calcium channel block, and inhibition of postsynaptic nicotinic or muscarinic receptors.²⁴¹

Tissue Damage

Repeated use of ketamine in high doses is associated with tissue damage. This relates not only to individuals that abuse ketamine (by snorting high doses of ketamine to induce a state of psychosis) but also to chronic pain patients treated with repeated and sometimes high ketamine doses. Increase in liver enzymes, allergic

hepatitis, cholangiopathy, hemorrhagic cystitis, thickening of the bladder wall, or renal damage may occur.^{[296,297](#)}

Allergic Reactions

Ketamine does not evoke the release of histamine and rarely, if ever, causes allergic reactions.^{[298](#)}

Platelet Aggregation

Ketamine inhibits platelet aggregation possibly by suppressed formation of inositol 1,4,5-triphosphate and subsequent inhibition of cytosolic free calcium concentrations.^{[299](#)} Drug-induced effects on platelet aggregation are a consideration in patients with known bleeding disorders undergoing surgery.

Emergence Delirium (Psychedelic Effects)

Emergence from ketamine anesthesia in the postoperative period may be associated with visual, auditory, proprioceptive, and confusional illusions, which may progress to delirium. Cortical blindness may be transiently present. Dreams and hallucinations can occur up to 24 hours after administration of ketamine. The dreams frequently have a morbid content and are often experienced in vivid color. Dreams and hallucinations usually disappear within a few hours.

Mechanisms

Emergence delirium probably occurs secondary to ketamine-induced depression of the inferior colliculus and medial geniculate nucleus, leading to misinterpretation of auditory and visual stimuli.^{[249](#)} Furthermore, the loss of skin and musculoskeletal sensations results in decreased ability to perceive gravity, thereby producing a sensation of bodily detachment or floating in space. Opioids that act as κ agonists produce similar psychedelic effects suggesting a potential role for ketamine interaction with κ receptors.

Incidence

The observed incidence of emergence delirium after ketamine ranges from 5% to 30% and is partially dose dependent.^{[249](#)} Factors associated with an increased incidence of emergence delirium include (1) age older than 15 years, (2) female gender, (3) doses of ketamine of greater than 2 mg/kg IV, and (4) a history of personality problems or frequent dreaming.^{[249](#)} In healthy volunteers, the incidence of psychedelic effects is related to the plasma concentration of ketamine (**Figure 5.28**).^{[300](#)} It is possible that the incidence of dreaming is similar in children, but this age group is less able to communicate the dream's occurrence. Indeed, there are reports of recurrent hallucinations in children as well as in adults receiving ketamine.^{[301,302](#)} Nevertheless, psychological changes in children after anesthesia with ketamine or inhaled drugs are not different.^{[303](#)} Likewise, no significant long-term personality differences are present in adults receiving ketamine compared with thiopental.^{[304](#)}

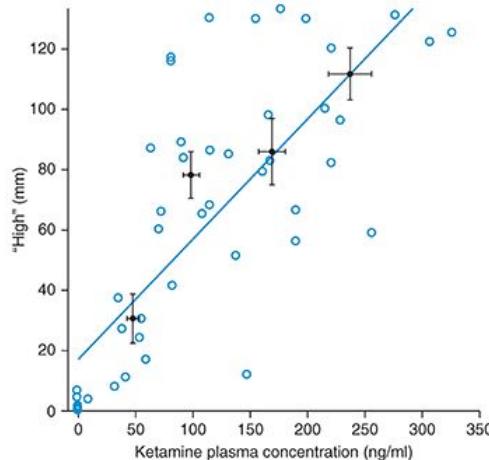


FIGURE 5.28 Visual analog scores for those patients experiencing ketamine-induced psychedelic effects (“high”) versus venous plasma concentrations of ketamine. Reprinted with permission from Bowdle TA, Radant AD, Cowley DS, et al. *Psychedelic effects of ketamine in healthy volunteers: relationship to steady-state plasma concentrations*. Anesthesiology. 1998;88(1):82-88. Copyright © 1998 American Society of Anesthesiologists, Inc.

Prevention

A variety of drugs used in preoperative medication or as adjuvants during maintenance of anesthesia have been evaluated in attempts to prevent emergence delirium after administration of ketamine. Benzodiazepines have proved the most effective in prevention of this phenomenon, with midazolam being more effective than diazepam.^{305,306} A common approach is to administer the benzodiazepine IV about 5 minutes before induction of anesthesia with ketamine. Inclusion of thiopental or inhaled anesthetics may decrease the incidence of emergence delirium attributed to ketamine. Conversely, the inclusion of atropine in the preoperative medication may increase the incidence of emergence delirium.³⁰⁷ Despite contrary opinions, there is no evidence that permitting patients to awaken from ketamine anesthesia in quiet areas alters the incidence of emergence delirium.³⁰⁸

Drug Interactions

The importance of an intact and normally functioning CNS in determining the cardiovascular effects of ketamine is emphasized by hemodynamic depression rather than stimulation that occurs when ketamine is administered in the presence of inhaled anesthetics. For example, depression by inhaled anesthetics of sympathetic nervous system outflow from the CNS prevents the typical increases in systemic blood pressure and heart rate that occur when ketamine is administered alone.²⁸⁹ Ketamine administered in the presence of volatile anesthetics may result in hypotension.³⁰⁹ Presumably, volatile anesthetics depress sympathetic nervous system outflow from the CNS, thus unmasking the direct cardiac depressant effects of ketamine. Diazepam, 0.3 to 0.5 mg/kg IV, or an equivalent dose of midazolam is also effective in preventing the cardiac-stimulating effects of ketamine. In the presence of verapamil, the blood pressure-elevating effects of ketamine may be attenuated, whereas drug-induced increases in heart rate are enhanced.³¹⁰ β -Blockade reduces ketamine-induced increase in heart rate and blood pressure.

Ketamine-induced enhancement of nondepolarizing neuromuscular blocking drugs may reflect interference by ketamine with calcium ion binding or its transport.³¹¹ Alternatively, ketamine may increase sensitivity of postjunctional membranes to neuromuscular blocking drugs. The duration of apnea after administration of succinylcholine is prolonged, possibly reflecting inhibition of plasma cholinesterase activity by ketamine.

Pharmacologic activation of adenosine triphosphate-regulated potassium channels mimics ischemic preconditioning and decreases infarct size or improves functional recovery of ischemic, reperfused viable (stunned) myocardium. Conversely, pharmacologic blockade of adenosine triphosphate-regulated potassium channels can antagonize the cardioprotective effects of ischemic preconditioning. In an animal model, ketamine blocked the cardioprotective effects of ischemic preconditioning and this effect was due to the R(-) isomer.³¹² Conversely, S(+) ketamine does not block the cardioprotective effects of preconditioning or alter myocardial infarct size (**Figure 5.29**).³¹³ In patients at risk for myocardial infarction during the perioperative period, drugs known to block preconditioning should be used with caution, whereas drugs known to elicit early and late preconditioning (opioids, volatile anesthetics) may be beneficial.

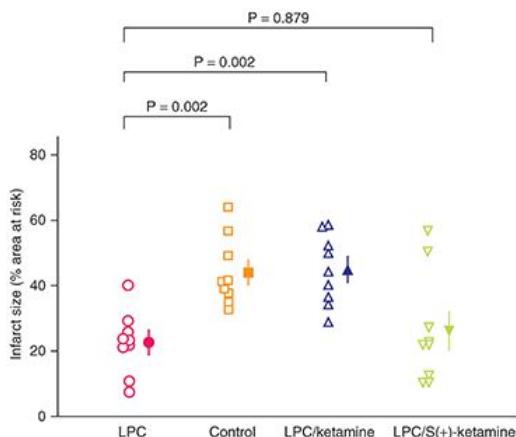


FIGURE 5.29 Infarct size as a percentage of the area at risk in late preconditioning (LPC), control, LPC/ketamine, and LPS/S(+) ketamine. Solid symbols represent mean \pm standard error of the mean. Reprinted with permission from Müllenheim J, Rulands R, Wietschorke T, et al. Late preconditioning is blocked by racemic ketamine, but not by S(+)-ketamine. Anesth Analg. 2001;93(2):265-270. Copyright © 2001 International Anesthesia Research Society.

Dextromethorphan

Dextromethorphan (*d*-isomer of levorphanol) is a low-affinity NMDA antagonist that is a common ingredient in over-the-counter cough suppressants. It also has activity at multiple other ligands including neuronal nicotinic receptors. It is equal in potency to codeine as an antitussive but lacks analgesic or physical dependence properties. Unlike codeine, this drug rarely produces sedation or gastrointestinal disturbances. Its euphoric effects lead to a significant abuse potential. Signs and symptoms of intentional excessive intake of dextromethorphan include systemic hypertension, tachycardia, somnolence, agitation, slurred speech, ataxia, diaphoresis, skeletal muscle rigidity, seizures, coma, and decreased core body temperature. Hepatotoxicity may be a consideration when dextromethorphan with acetaminophen is ingested in excessive amounts.

Dexmedetomidine

Dexmedetomidine is a highly selective, specific, and potent α_2 -adrenergic agonist (1,620:1 α_2 to α_1).^{314,315} One of the highest densities of α_2 receptors is present in the pontine locus coeruleus, an important source of sympathetic nervous system innervation of the forebrain and a vital modulator of vigilance. The sedative effects evoked by dexmedetomidine most likely reflect inhibition of this nucleus.³¹⁶

Dexmedetomidine is the dextroisomer and pharmacologically active component of medetomidine, which has been used for many years in veterinary practice for its hypnotic, sedative, and analgesic effects. Compared with clonidine, dexmedetomidine is 7 to 10 times more selective for α_2 receptors and has a shorter duration of action than clonidine. In this regard, dexmedetomidine is considered a full agonist at the α_2 receptor, whereas clonidine is a partial agonist (ratio of α_2 to α_1 activity for clonidine is 220:1).³¹⁵

Atipamezole is a specific and selective α_2 -receptor antagonist that rapidly and effectively reverses the sedative and cardiovascular effects of IV dexmedetomidine.³¹⁷ Atipamezole as an emergency treatment for overdose of α_2 agonists used in zoo and wildlife anesthesia and is not currently available for human use.³¹⁸

The quality of sedation produced by α_2 agonists differs from sedation produced by drugs (midazolam, propofol) that act on GABA.³¹⁹ For example, dexmedetomidine, acting on α_2 receptors, produces sedation by decreasing sympathetic nervous system activity and the level of arousal. The result is a calm patient who can be easily aroused to full consciousness. Amnesia is not assured. Drugs that activate GABA receptors produce a clouding of consciousness and can cause paradoxical agitation as well as tolerance and dependence.

Pharmacokinetics

The elimination half-time of dexmedetomidine is 2 to 3 hours compared with 6 to 10 hours for clonidine. Dexmedetomidine is highly protein bound (>90%) and undergoes extensive hepatic metabolism. The resulting methyl and glucuronide conjugates are excreted by the kidneys. Dexmedetomidine has weak inhibiting effects on cytochrome P450 enzyme systems that might manifest as increased plasma concentrations of opioids as administered during anesthesia.³²⁰

Clinical Uses

As with clonidine, pretreatment with dexmedetomidine attenuates hemodynamic responses to tracheal intubation, decreases plasma catecholamine concentrations during anesthesia, decreases perioperative requirements for inhaled anesthetics and opioids, and increases the likelihood of hypotension.^{321,322} Dexmedetomidine decreases MAC for volatile anesthetics in animals by greater than 90% compared with a plateau effect between 25% to 40% for clonidine (**Figure 5.30**).³²³ In patients, isoflurane MAC was decreased 35% and 48% by dexmedetomidine plasma concentrations of 0.3 and 0.6 ng/mL, respectively.³²⁴ Despite marked dose-dependent analgesia and sedation produced by this drug, there is only mild depression of ventilation. Dexmedetomidine in high doses (loading dose of 1 µg/kg IV followed by 5-10 µg/kg/hour IV) produces total IV anesthesia without associated depression of ventilation.³²⁵ The preservation of breathing provides a potential anesthetic technique for patients with a difficult upper airway. More recent evidence suggests that light to moderate sedation with dexmedetomidine does not offer any protection from central apnea or upper airway collapse when compared with similar levels of sedation provided with propofol.³²⁶ As with clonidine, dexmedetomidine has been reported to be effective in attenuating the cardiotonulatory and postanesthetic delirium effects of ketamine.³²⁷ Addition of 0.5 µg/kg dexmedetomidine to lidocaine being administered to produce IV regional anesthesia improves the quality of anesthesia and postoperative analgesia without causing side effects.³²⁸ Dexmedetomidine markedly increases the range of temperatures not triggering thermoregulatory defenses. For this reason, dexmedetomidine, like clonidine, is likely to promote perioperative hypothermia and also prove to be an effective treatment for nonthermally induced shivering.³²⁹ Severe bradycardia may follow the rapid infusion of dexmedetomidine, and cardiac arrest has been reported in a patient receiving a dexmedetomidine infusion as a supplement to general anesthesia.³³⁰

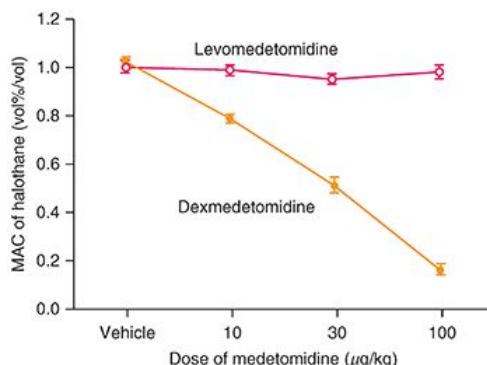


FIGURE 5.30 Dexmedetomidine produces dose-dependent decreases in halothane minimum alveolar concentration (MAC) in rats. Levomedetomidine did not produce any changes in MAC. Data are mean ± standard error of the mean. *Reprinted with permission from Segal IS, Vickery RG, Walton JK, et al. Dexmedetomidine diminishes halothane anesthetic requirements in rats through a postsynaptic alpha-2 adrenergic receptor. Anesthesiology. 1988;69(6):818-823. Copyright © 1988 American Society of Anesthesiologists, Inc.*

Postoperative Sedation

Dexmedetomidine (0.2-0.7 µg/kg/hour IV) is useful for sedation of postoperative critical care patients in an ICU environment, particularly when mechanical ventilation via a tracheal tube is necessary. In comparison

with remifentanil, dexmedetomidine infusions do not result in clinically significant depression of ventilation and sedation exhibits some similarity with natural sleep.³³¹ Following tracheal extubation, dexmedetomidine-sedated patients breathe spontaneously and appear calm and relaxed.³³² Both clonidine and dexmedetomidine are useful in the ICU to prevent drug withdrawal symptoms following long-term sedation with benzodiazepines. Because of its sympatholytic and vagomimetic actions, dexmedetomidine may be accompanied by systemic hypotension and bradycardia. The ability to specifically antagonize the sedative effects of dexmedetomidine with atipamezole may be useful.³¹⁷

Effects on the Control of Breathing

Dexmedetomidine is promoted as a sedative with minimal impact on the control of breathing and the upper airway musculature. However, in common with propofol, dexmedetomidine reduces the ventilatory response to hypoxia, while resting ventilation may be minimally affected.³³³ Additionally, dexmedetomidine does not protect the upper airways against obstruction.³³³ These are important observations, as a reduction of ventilatory drive together with a tendency toward upper airway collapse is a potentially life-threatening effect that may further be aggravated by the concomitant use of opioids.

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Pain Physiology

Hui Yang • Bihua Bie • Mohamed A. Naguib[†]

Pain is a complex phenomenon and includes both sensory-discriminative and motivational-affective components.¹ The sensory-discriminative component of pain depends on ascending projections of tracts (includes the spinothalamic and trigeminothalamic tracts) into the cerebral cortex. Sensory processing at these higher levels results in the perception of the quality of pain (pricking, burning, aching), the location of the painful stimulus, the intensity of the pain, and the duration of the pain. The motivational-affective responses to painful stimuli include attention and arousal, somatic and autonomic reflexes, endocrine responses, and emotional changes. These account collectively for the unpleasant nature of painful stimuli.

The definition of pain as accepted by the International Association for the Study of Pain (IASP) emphasizes the complex nature of pain as a physical, emotional, and psychological condition. It is recognized that pain does not necessarily correlate with the degree of tissue damage that is present. Failure to appreciate the complex factors that affect the experience of pain and reliance entirely on physical examination findings and laboratory tests may lead to misunderstanding and inadequate treatment of pain. Oversimplified anatomic concepts predispose to simplistic therapeutic interventions, such as neurectomy or rhizotomy that may intensify pain or create new and often more distressing pain.

In reality, the nociceptive system is highly complex and highly adaptable. Sensitivity of most of its components can be reset by a variety of physiologic and pathologic conditions. Innovative medications are being developed that target the causes of pain by actions on pain transduction, transmission, interpretation, and modulation in both the peripheral nervous system (PNS) and the central nervous system (CNS).

Social Impact

Pain is one of the most common reasons for visiting a physician. It is estimated that chronic pain may affect as many as 40% of the adult population.² The prevalence of low back pain ranges from 8% to 37% and is particularly prominent in patients between 45 and 60 years of age. It is estimated that 40 million persons experience musculoskeletal pain conditions.³ Patients with malignant disease often experience increasing pain because their disease progresses. The costs to society related to chronic pain are immense with an estimate that the annual cost attributed to back pain, migraine headache, and arthritis alone is 40 billion dollars (not including surgical procedures to treat pain, lost workdays).¹

Neurobiology of Pain

The experience of pain involves a series of complex neurophysiologic processes that reflect four distinct components: transduction, transmission, modulation, and perception. Modulation of pain is the process of altering pain transmission. It is likely that both inhibitory and excitatory mechanisms modulate pain (nociceptive) impulse transmission in the PNS and CNS. Pain perception is thought to occur at the thalamus, with the cortex being important for discrimination of specific sensory experiences.¹ Pain may occur in the absence of the occurrence of these four steps. For example, pain from trigeminal neuralgia occurs in the absence of transduction of a chemical stimulus at a nociceptor reflecting axonal discharges initiated at the site of a compressed or demyelinated nerve. Modulation of pain impulses may not occur if specific nervous system tracts are injured. For example, phantom limb pain occurs in the absence of nociception or nociceptors (pain receptors).

Peripheral Nerve Physiology of Pain

Nociceptors (Pain Receptors)

Nociceptors are a specialized class of primary afferents that respond to intense, noxious stimuli in skin, muscles, joints, viscera, and vasculature. Nociceptors are distinctive in that they typically respond to the multiple energy forms that produce injury (thermal, mechanical and chemical stimuli) and provide information to the CNS regarding the location and intensity of noxious stimuli. In normal tissues, nociceptors are inactive until they are stimulated by sufficient energy to reach the stimulus (resting) threshold. Thus, nociceptors prevent random signal propagation (screening function) to the CNS for the interpretation of pain.

Specific types of nociceptors react to different types of stimuli. Generally, unmyelinated C-fiber afferents (conduction velocity <2 m/s) have receptive field about 100 mm^2 in human and signal the burning pain from intense heat stimuli applied to the glabrous skin as well as the pain from sustained pressure. Two types of myelinated A-fiber nociceptive afferents (conduction velocity >2 m/s) exist. Type I fibers (including $\text{A}\beta$ and some $\text{A}\delta$ fibers) are typically high-threshold mechanoreceptors and are also usually responsive to heat, mechanical, and chemical stimuli and may therefore be referred to as **polymodal nociceptors**. Type II fibers ($\text{A}\delta$ fibers with lower conduction velocity about 15 m/s) have no demonstrable response to mechanical stimuli and are thought to signal first pain sensation from heat stimuli. Both myelinated and unmyelinated nociceptors signal pain from chemical and cold stimuli.

Sensitization of Nociceptor

Sensitization of nociceptors refers to their increased responsiveness to heat, cold, mechanical, or chemical stimulation that gives rise to primary hyperalgesia to these stimuli.⁴ Sensitization of nociceptors frequently occurs, which was attributable to the increased inflammatory mediators and adaptation of signaling pathways in primary sensory neurons induced by noxious stimuli. In the majority of cases of acute inflammation, the process naturally resolves as tissues heal, peripheral sensitization diminishes, and nociceptors return to their original resting threshold. Chronic pain, however, occurs if the conditions associated with inflammation do not resolve, resulting in sensitization of peripheral and central pain signaling pathway and increased pain sensations to normally painful stimuli (hyperalgesia) and the perception of pain sensations in response to normally nonpainful stimuli (allodynia).

Numerous endogenous chemicals and mediators significantly contribute to the induction of nociception during peripheral inflammation and nerve injury. Most of these mediators are not constitutively stored but synthesized **de novo** at the site of injury. The agents contribute to pain via two principal mechanisms. Some of these agents (eg, bradykinin, protons, prostaglandin E₂, purines, and cytokines) can directly activate nociceptors and/or induce the sensitization of the nociceptor response to painful stimuli, whereas others (eg, serotonin, histamine, arachidonic acid metabolites, and cytokines) may act indirectly to activate the inflammatory cells, which in turn release cytokines to induce the primary hyperalgesia. The chemical mediators released during inflammation can have a synergistic effect in potentiating nociceptor responses (**Figure 6.1**).⁵ For example, bradykinin have the potency to directly activate the peripheral nociceptors, whereas other mediators such as prostaglandins have the potency to sensitize the nociceptors and make them hyperresponsive to peripheral stimulation.⁵

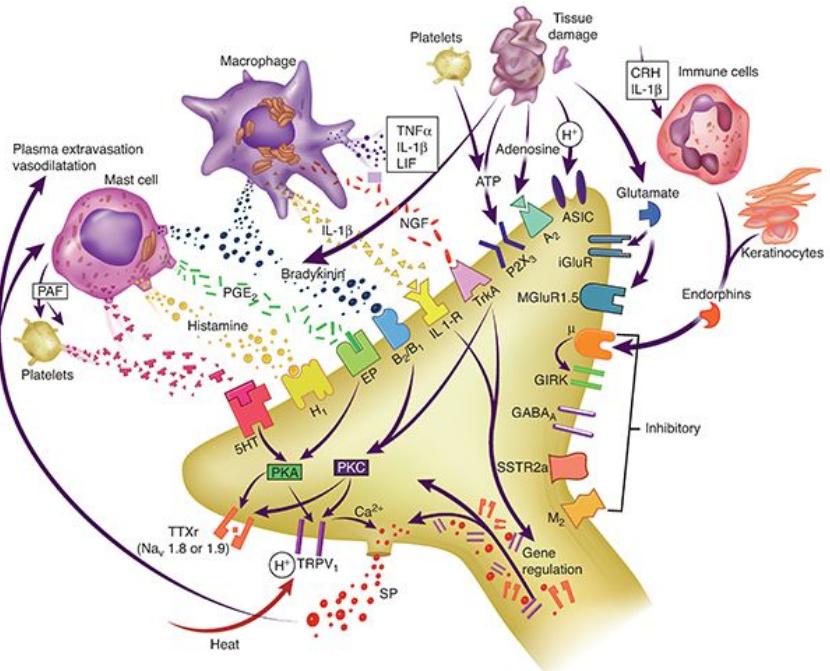


FIGURE 6.1 Cellular mechanisms underlying nociceptor sensitization induced by peripheral inflammation. Activated immune cells (macrophages, mast cells, and other immune cells) and injured cells release numerous chemicals, which may directly or indirectly sensitize the peripheral nerve terminals. Abbreviations: A₂, adenosine A₂ receptor; ASIC, acid-sensing ion channel; ATP, adenosine triphosphate; B₂/B₁, bradykinin receptor B₂/B₁; Ca²⁺, calcium ion; CRH, corticotrophin-releasing hormone; EP, E-prostanoid receptor; GABA_A, gamma-aminobutyric acid receptor type A; GIRK, G-protein-coupled inward rectifying potassium channel; H⁺, hydrogen ion; H₁, histamine H₁ receptor; 5HT, serotonin; iGluR, ionotropic glutamate receptor; IL-1 β , interleukin-1 β ; IL 1-R, interleukin-1 receptor; LIF, leukemia inhibitory factor; M₂, muscarinic receptor; MGlur, metabotropic glutamate receptor; μ , μ -opioid receptor; Na_v, voltage-gated sodium channel; NGF, nerve growth factor; P2X₃, purinergic receptor P2X ligand-gated ion channel 3; PAF, platelet-activating factor; PGE₂, prostaglandin E₂; PKA, protein kinase A; PKC, protein kinase C; SP, substance P; SSTR2a, somatostatin receptor 2a; TNF α , tumor necrosis factor α ; TrkA, tyrosine kinase receptor A; TRPV₁, transient receptor potential vanilloid receptor 1; TTXr, tetrodotoxin-resistant sodium channel. Reprinted from McMahon SB, Koltzenburg M. Wall and Melzack's Textbook of Pain. 5th ed. Edinburgh: Churchill Livingstone; 2006. Figure 1.14. Copyright © 2006 Elsevier. With permission.

A variety of receptors and ion channels have been identified on dorsal root ganglion neurons and on peripheral terminals of nociceptive afferent fibers. These receptors, including purinergic,⁶ metabotropic glutamatergic, tachykinin,⁷ transient receptor potential vanilloid receptor 1 receptor and neurotrophic receptors, and ion channels (eg, Nav1.8) in primary sensory neurons, may also undergo significant adaptation after exposure to noxious stimuli, which significantly lowers the firing threshold of nociceptor and critically contributes to the induction and maintenance of primary hyperalgesia.⁸

Primary Hyperalgesia and Secondary Hyperalgesia

In general, tissue injury and inflammation may activate a cascade of events leading to enhanced pain in response to noxious stimuli, which is termed as **hyperalgesia**. Hyperalgesia is defined as a leftward shift of the stimulus-response function that relates magnitude of pain to stimulus intensity. Hyperalgesia is a consistent feature of somatic and visceral tissue injury and inflammation. Hyperalgesia at the original site of injury is termed **primary hyperalgesia**, and hyperalgesia in the uninjured skin surrounding the injury is

termed **secondary hyperalgesia**. Primary hyperalgesia is usually manifested as decreased pain threshold, increased response to suprathreshold stimuli, spontaneous pain, and expansion of receptive field. Although primary hyperalgesia is characterized by the presence of enhanced pain from heat *and* mechanical stimuli, secondary hyperalgesia is characterized by enhanced pain response to *only* mechanical stimuli. It is usually accepted that interaction between the proinflammatory mediators and their receptors in nociceptors leads to the induction of primary hyperalgesia, and sensitization of central neurocircuits processing nociceptive information may account for the secondary hyperalgesia after tissue injury.

Central Nervous System Physiology

Pain transmission from peripheral nociceptors to the spinal cord and higher structures of the CNS is a dynamic process involving several pathways, numerous receptors, neurotransmitters, and secondary messengers. The spinal dorsal horn functions as a relay center for nociceptive and other sensory activity. The ascending pathways convey pain-related activity to the brainstem and forebrain in humans. Forebrain somatosensory cortices (SI and SII) account for the perception of sensory-discriminative of peripheral painful stimuli, and some brain regions in the limbic cortex and thalamus account for the perception of motivational-affective components of pain.^{9,10} Descending projections originating from periaqueductal gray (PAG)-RVM (rostral ventromedial medulla) system may either depress or facilitate the integration of painful information in the spinal dorsal horn ([Figure 6.2](#)).

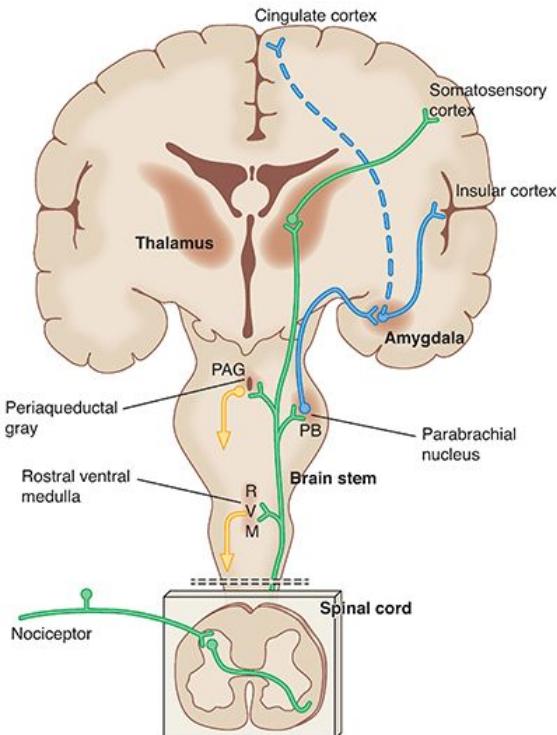


FIGURE 6.2 The projection pathway for the transmission of pain information into the brain. Primary afferent nociceptors convey noxious information to projection neurons within the dorsal horn of the spinal cord. A subset of these projection neurons transmits information to the somatosensory cortex via the thalamus, providing information about the location and intensity of the painful stimulus. Other projection neurons engage the cingulate and insular cortices via connections in the brainstem (parabrachial [PB] nucleus) and amygdala, contributing to the affective component of the pain experience. This ascending information also accesses neurons of the rostral ventromedial medulla (RVM) and midbrain periaqueductal gray (PAG) to engage descending feedback systems that regulate the output from the spinal cord. *Reprinted from Basbaum AI, Bautista DM, Scherrer G, et al. Cellular and molecular mechanisms of pain. Cell. 2009;139(2):267-284. Copyright © 2009 Elsevier. With permission.*

The Dorsal Horn: The Relay Center for Nociception

Afferent fibers from peripheral nociceptors enter the spinal cord in the dorsal root, ascend or descend several segments in the Lissauer tract, and synapse with the dorsal horn neurons for the primary integration of peripheral nociceptive information. The dorsal horn contains four major neuronal components: the central terminals of primary afferent axons; intrinsic neurons, which are terminating locally or extending into other spinal segments; projection neurons that are passing rostrally in the white matter to reach various parts of the brain; and descending axons that pass caudally from several brain regions and play an important role in modulating the integration of nociceptive information.

The central terminals of primary afferents occupy highly ordered spatial locations in the dorsal horn. The dorsal horn consists of six laminae (Figure 6.3). Laminae I (marginal layer) and II (substantia gelatinosa) are often referred to as the **superficial dorsal horn** and serve as main target of afferent C fibers. Lamina I contains both projection neurons and interneurons, and all of the neurons in lamina II are small interneurons. Lamina V is the site of second-order wide dynamic range and nociceptive-specific neurons that receive input from nociceptive and nonnociceptive neurons. The nociceptive-specific neurons respond only to noxious stimuli in their peripheral environment, whereas wide dynamic range neurons respond to innocuous and noxious stimuli of many types. Both types of neurons are believed to be important in the perception of nociceptive information. Myelinated fibers innervating muscles and viscera terminate in laminae I, IV to VII, and the ventral horn, and the unmyelinated fibers from these organs mostly terminate in laminae I, II, and V as well as X.

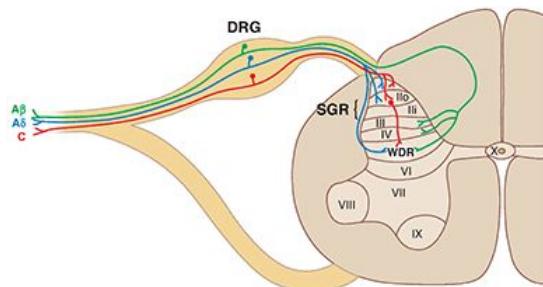


FIGURE 6.3 Schematic representation of the spinal projections of primary afferent fibers. In general, unmyelinated C fibers synapse with the interneurons laminae I (marginal layer) and II (substantia gelatinosa of Rolando [SGR]). Cutaneous A_D fibers usually project to laminae I, II, and V, and A_B fibers primarily terminate in laminae III, IV, V in dorsal horn. Large-diameter myelinated fibers innervating muscles, joint, and viscera may also terminate in laminae I, IV to VII, and the ventral horn. Second-order wide dynamic range (WDR) neurons are located in lamina V and receive input from nociceptive and nonnociceptive neurons. Abbreviation: DRG, dorsal root ganglia.

Interneurons make up the great majority of the neuronal population throughout the dorsal horn. Many dorsal horn interneurons have axons that remain in the same lamina as the cell body, and they also give rise to axons that extend into other laminae. Interneurons in the dorsal horn can be divided into two main functional types: inhibitory cells, which use γ -aminobutyric acid and/or glycine as their principal transmitter, and excitatory glutamatergic cells. Interneurons in dorsal horn are important for integration and modulation of incoming nociceptive information.

Projection neurons with axons that project to the brain are present in relatively large numbers in lamina I and are scattered through the deeper part of the dorsal horn (laminae III-VI) and the ventral horn. Both the lamina I and the laminae III to IV projection neurons that express the neurokinin 1 receptor are heavily innervated by substance P-containing primary afferents. Those in lamina I, together with some of the projection cells in deeper laminae, have axons that cross the midline and ascend to a variety of supraspinal targets including the thalamus, the midbrain periaqueductal gray matter, lateral parabrachial area of the pons, and various parts of the medullary reticular formation.

Two types of descending monoaminergic (serotonergic and norepinephrinergic) axons project from the brain throughout the dorsal horn, mostly terminating in laminae I and II, and are involved in descending pain modulation. Serotonergic axons in the spinal cord originate in the medullary raphe nuclei, whereas those that contain norepinephrine are derived from cells in the locus coeruleus and adjacent areas of the pons.

Gate Theory

The gate control theory of pain was first proposed by Ronald Melzack and Patrick Wall in 1965 to illustrate the neuronal network underlying pain modulation (a neurologic “gate”) in the spinal dorsal horn. According to this theory, painful information is projected to the supraspinal brain regions if the gate is open, although painful stimulus is not felt if the gate is closed by the simultaneous inhibitory impulses ([Figure 6.4](#)). Here is a commonly used example to describe how this neuronal network modulates pain transmission. Usually, rubbing the skin of painful area seems to somehow relieve the pain associated with a bumped elbow. In this case, rubbing the skin activates large-diameter myelinated afferents (A β), which is “faster” than A δ fibers or C fibers conveying painful information. These A β fibers deliver information about pressure and touch to the dorsal horn and overrides some of the pain messages carried by the A δ and C fibers by activating the inhibitory interneurons in the dorsal horn. This hypothesis provided a practical theoretical basis for some approaches such as massage, transcutaneous nerve stimulation, and acupuncture to effectively treat pain in clinical patients.[11-13](#)

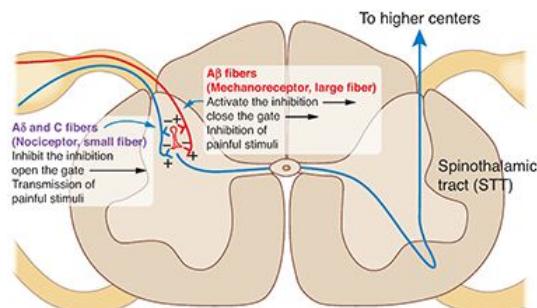


FIGURE 6.4 The illustration of gate theory for pain modulation in spinal dorsal horn. Usually, rubbing the skin of painful area seems to somehow relieve the pain associated with a bumped elbow. Large-diameter myelinated afferents (A β) conveying pressure and touch information have “faster” transduction speed than A δ fibers or C fibers conveying painful information to the dorsal horn. Once appropriate peripheral mechanical stimuli are applied, the excited A β fibers may activate the inhibitory interneurons in the dorsal horn and then somehow override the pain messages carried by the A δ and C fibers.

Central Sensitization of Dorsal Horn Neurons

Peripheral inflammation and nerve injury could alter the synaptic efficacy and induce central sensitization in the dorsal horn neurons, which is considered as a fundamental mechanism underlying the induction and maintenance of chronic pain. This central sensitization takes a number of different and distinct forms.[14](#) The first form of central sensitization is windup of dorsal horn neurons, an activity-dependent progressive increase in the response of neurons over the course of a train of inputs. The second form of central sensitization is a heterosynaptic activity-dependent plasticity that outlasts the initiating stimulus for tens of minutes, in which, following a brief (as short as 10-20 seconds) intense nociceptor-conditioning stimulus, normally subliminal/subthreshold inputs can activate dorsal horn neurons as a result of an increase in synaptic efficacy. Other forms of central sensitization include long-term potentiation, transcription-dependent central sensitization, loss of inhibition, and rearrangement of synaptic contacts. Therefore, central sensitization represents an abnormal state of responsiveness or increased gain of the processing of nociceptive information and pain sensation. Central sensitization is not essentially coupled with the presence, intensity, or duration of individual peripheral stimuli. This is well exemplified by the clinical observations that patients suffering from

neuropathic pain usually exhibit painful response to nonnoxious stimuli, exaggerated or sustained response to a noxious stimulus, and/or painful sensitivity in surrounding normal tissues.¹⁵

Ascending Pathway for Pain Transmission

Ascending pathways from the spinal cord to sites in the brainstem and thalamus are important for the perception and integration of nociceptive information. The major ascending pathways important for pain include the spinothalamic tract (STT, direct projections to the thalamus), spinomedullary and spinobulbar projections (direct projections to homeostatic control regions in the medulla and brainstem), and spinohypothalamic tract (direct projections to the hypothalamus and ventral forebrain). Some indirect projections, such as the dorsal column system and the spinocervicothalamic pathway, also exist to forward nociceptive information to the forebrain through the brainstem. Similar pathways originating from the medulla trigeminal sensory nuclei also exist to process the nociceptive information from the facial structures.

Among these pathways, STT is the most closely associated with pain, temperature, and itch sensation. The STT originates in the spinal dorsal horn neurons in lamina I (receiving input from small-diameter A δ and C primary afferent fibers), laminae IV to V (receiving input primarily from large-diameter A β fibers from skin), and laminae VII to VIII (receiving convergent input from large-diameter skin and muscle, joint inputs). About 85% to 90% of STT cells are found on the contralateral side, with 10% to 15% on the ipsilateral side. The axons of STT cells generally cross in the dorsal and ventral spinal commissures to reach the white matter of the contralateral spinal cord within one or two segments rostral to the cells of origin. The axons of STT terminate in several distinct regions of the thalamus.

Supraspinal Modulation of Nociception

Several brain areas are gradually defined with human brain imaging studies as key supraspinal regions involved in nociceptive perception. The most commonly activated regions during acute and chronic pain include SI, SII, anterior cingulate cortex (ACC), insular cortex (IC), prefrontal cortex, thalamus, and cerebellum (see [Figure 6.2](#)). These brain regions form a cortical and subcortical network, which are critically involved in the formation of emotional aspects of pain and the central modulation of pain perception.

In primate, SI and SII receive noxious and innocuous somatosensory input from somatosensory thalamus.¹⁶ Cingulate cortex receives input from medial thalamic nuclei that contain nociceptive neurons, including nucleus parafascicularis and the ventrocaudal part of nucleus medialis dorsalis as well as from lateral thalamic regions. The IC also receives direct thalamocortical nociceptive input in the primate. The prefrontal cortex receives input from ACC, without direct thalamocortical nociceptive input. In general, somatosensory cortices (eg, SI and SII) are more important for the perception of sensory features (eg, the location and duration of pain), whereas limbic and paralimbic regions (eg, ACC and IC) are more important for the emotional and motivational aspects of pain.¹⁷

Descending Pathway for Pain Modulation

It is well recognized that descending pathways originating from certain supraspinal regions may concurrently promote and suppress nociceptive transmission in the dorsal horn, which were termed as descending inhibition pathway and descending facilitation pathway.¹⁸ Among these brain regions, PAG and consequent rostral ventromedial medulla (RVM) brainstem serve as the critical brain regions underlying descending pain modulation ([Figure 6.5](#)). The PAG neurons receive direct or indirect inputs from several brain structures, including amygdala, nucleus accumbens, hypothalamus, and others, with ascending nociceptive afferents from the dorsal horn. The PAG and the adjacent nucleus cuneiformis are the major source of inputs to the RVM. The RVM also receives an input from serotonin-containing neurons of the dorsal raphe and neurotensinergic neurons of the PAG. The PAG projects only minimally to the spinal cord dorsal horn, and the pain-modulating action of the PAG on the spinal cord is relayed largely, if not exclusively, through the RVM. Electrical stimulation of the RVM at different currents can produce inhibition or facilitation of dorsal horn nociceptive processing, which suggesting that there are parallel inhibitory and facilitatory output pathways from RVM to spinal dorsal horn (see [Figure 6.5](#)).¹⁹ It is also important to note that PAG-RVM system serves as one of the major brain sites underlying opiates-induced analgesia.²⁰ μ -Opioid receptor is

widely expressed in the descending pain modulatory pathway, including the PAG, RVM, and the dorsal horn neurons. Activation of μ -opioid receptor in PAG by exogenous or endogenous opioids decreases the activity of GABAergic neurons in PAG resulting in disinhibition of RVM neurons in descending inhibition pathway and subsequent suppression the neuronal activity in dorsal horn neurons.²¹

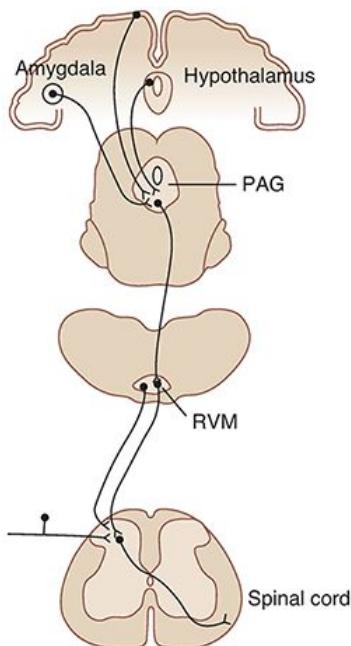


FIGURE 6.5 Properties of proposed medullary pain-modulating neurons. Single-unit extracellular recording was performed by microelectrode in the rostral ventromedial medulla (RVM) while peripheral noxious stimuli (heat) were applied. As shown by the oscilloscope sweeps, the firing of the off cell pauses just prior to the tail flick reflex (indicating pain sensation) in response to noxious heat, although the typical on-cell firing occurs before the tail flick. The diagram illustrates that both on and off cells project to the spinal cord, where they exert bidirectional control over nociceptive dorsal horn neurons. Abbreviation: PAG, periaqueductal gray. Reprinted from McMahon SB, Koltzenburg M. Wall and Melzack's Textbook of Pain. 5th ed. Edinburgh: Churchill Livingstone; 2006. Figure 7.2. Copyright © 2006 Elsevier. With permission.

Spinally projecting noradrenergic neurons of the pontine tegmentum contribute significantly to pain modulation. The locus coeruleus and the A5 and A7 noradrenergic cell groups are the major source of noradrenergic projections to the dorsal horn. Electrical stimulation in each of these regions produces behavioral analgesia and inhibition of dorsal horn neurons mediated by spinal α_2 -adrenergic receptors.

Transition From Acute Pain to Chronic Pain

Acute pain is a short-term pain; when pain receptors no longer detect any tissue damage, the pain sensations would stop. Acute pain does not persist after the initial injury has healed. In contrast, chronic pain is persistent pain beyond the expected period of healing. In this case, pain receptors continue to fire, even in the absence of tissue damage. There may no longer be a physical cause of pain, but the pain response is there. The distinction between acute and chronic pain is not definitely delineated by any clear-cut time interval, although two cutoff points, 3 months and 6 months, are often practically used. Despite recent improvements in techniques for acute pain management, chronic pain still develops in a significant proportion of patients with surgical procedures.

Sensitization of peripheral and central nocisponsive neurons (eg, neurokinin 1 receptor positive dorsal horn neurons) underlies the neurobiologic basis of the transition from acute pain to chronic pain; negative psychological experience during acute pain and noxious stimuli-induced epigenetic modification²² in PNS and CNS are also critically involved in the induction and maintenance of chronic pain. Recent studies suggest

that patients with subacute low back pain who are having negative affective experience (depression and maladaptive cognition) develop greater functional connectivity of the nucleus accumbens with prefrontal cortex; the brain regions processing emotion and rewarding are prone to develop persistent pain.^{23,24}

In the dorsal horn, activated microglia play a substantial role in pain transition from acute to persisted status after peripheral nerve injury or inflammation.²⁵ Peripheral nerve injury induces de novo expression of colony-stimulating factor 1 (CSF1) in injured sensory neurons, which is subsequently transported to the spinal cord and targeted the microglial CSF1 receptor (CSF1R). This CSF1-mediated signaling eventually induces the microglia activation and central sensitization in the dorsal horn and contribute to the transition from acute pain to chronic pain.²⁶ Furthermore, interaction between microglia and nocisponsive dorsal horn neurons, via various chemokines (eg, CX3CL1), cytokines (eg, interleukin-6), and their receptors, epigenetically regulates the expression of various proteins (eg, CXCL12) and enhances the neuronal excitability in dorsal horn in the setting of neuropathic pain.²⁷ Microglia activation appears to be critical in the transition of acute pain to chronic pain. Other molecular and cellular mechanisms (eg, epigenetic modification and neuronal hypersensitivity in peripheral and the dorsal horn neurons) appear to play a role in the transition from acute pain to chronic pain.^{28,29}

Psychobiology of Pain

Pain is defined by the IASP as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.” Discomfort, fear of pain, and anxiety are the most often psychological symptom observed in the patients suffering from pain, although other aversive emotional qualities, including depression, anger, disgust, and guilt, are not unusual in these patients.

Affective qualities of pain are transmitted and processed in the same pathways as those for the painful sensory transmission. The peripheral nociceptive information is delivered through spinoreticular pathways to diencephalic and telencephalic structures, including the medial thalamus, hypothalamus, amygdala, and limbic cortex. Central sensitization and adaptation of synaptic plasticity occur in these brain regions and contribute to the induction and maintenance of the emotional distress resulting from the pain.¹⁷

It appears that intrinsic interactions occur between the sensory and affective components of pain. Although the affective qualities of painful experience vary across individuals, most patients experiencing acute or chronic pain display substantial emotional, behavioral, or social abnormalities during the onset of pain. Although these affective symptoms may gradually wane and relatively undergo adaptation in some patients, a substantial proportion of patients with chronic pain may display debilitating depression, anxiety, cognitive deficiency, and other negative psychological components of pain. On the other hand, severe emotional distress can trigger new pain or exacerbate the ongoing pain in the patients with previous painful experience.³⁰

Some Specific Types of Pain

Neuropathic Pain

Neuropathic pain, characterized by a reduced nociceptive threshold, persists in the absence of a stimulus and is refractory to traditional analgesics. Injury of peripheral nerves by trauma, surgery, or diseases (eg, diabetes) frequently results in the development of neuropathic pain. Cancer patients are at increased risk of neuropathic pain caused by radiotherapy or a variety of chemotherapeutic agents. Although acute and inflammatory pain are usually considered as an adaptive process of the pain system to provide warning and protection, neuropathic pain actually reflects a maladaptive (pathophysiologic) function of a damaged pain system. In many patients, neuropathic pain persists throughout life and negatively affects physical, emotional, and social quality of life.³¹ There is currently no effective symptomatic treatment for neuropathic pain. Opioids, gabapentin, amitriptyline, and medicinal cannabis preparations have appear to have limited efficacy.³²⁻³⁴ The pathophysiologic process of neuropathic pain has the hallmarks of a neuroinflammatory response following innate immune system activation. Toll-like receptors 2 and 4 on microglia appear to trigger glial activation, initiating proinflammatory and signal transduction pathways^{35,36} that lead to the production of

proinflammatory cytokines. Central cannabinoid receptor type 2 appears to play a protective role, and administration of a cannabinoid receptor type 2 receptor agonist can blunt the neuroinflammatory response and prevent peripheral neuropathy through interference with specific signaling pathways.^{37,38}

The common pathologic features of the neural damage include segmental dysmyelination/demyelination and axonopathy, ranging from metabolic and axoplasmic transport deficits to frank transection of the axon (axotomy). After nerve injury occurs, the proximal stump of axon seals off and forms a terminal swelling or “end bulb,” and numerous fine processes (“sprouts”) start to grow out from the end bulb in 1 or 2 days. These regenerating sprouts normally elongate within their original endoneurial tube and restore the normal sensation in appropriate peripheral targets. However, in case the forward growth is blocked, such as after limb amputation, end bulbs and aborted sprouts form a tangled mass at the nerve end, a “nerve-end neuroma.” Usually, the ectopic firing generated in end bulb and sprouts in neuroma, as well as the cell bodies in dorsal root ganglia, significantly contribute to the nociceptive hypersensitivity and ectopic mechanosensitivity–induced nerve injury.

Visceral Pain

Although somatic pain is easily localized and characterized by distinct sensations, visceral pain is diffuse and poorly localized, typically referred to somatic sites (eg, muscle and skin), and it is usually associated with stronger emotional and autonomic reactions. Also, visceral pain is often produced by stimuli different from those adequate for activation of somatic nociceptors. These features may be attributable to dual nerve innervation and the unique structure of receptive ending.

Among all tissues in the body, the viscera are unique in that each organ receives innervation from two sets of nerves, either vagal and spinal nerves or pelvic parasympathetic nerves, and the visceral afferent innervation is sparse relative to somatic innervation. Spinal visceral afferent fibers have their cell bodies in dorsal root ganglia and terminate in the spinal dorsal horn. The central termination of visceral afferents synapse spinal neurons in laminae I, II, V, and X over several segments and deliver the visceral sensory information through the contralateral STT or ipsilateral dorsal column to supraspinal brain sites. These spinal neurons also receive convergent input from somatic (or another visceral) structures, providing the structural basis for referred pain. Another set of nerve system conveying pain information of organs in the thoracic and abdominal cavities is the vagus nerve, which has cell bodies in the nodose ganglion and central terminals in the nucleus tractus solitarii. The vagus afferent innervation plays an important role in the prominent autonomic and emotional reactions in visceral diseases associated with pain (**Figure 6.6**). The majority of visceral afferent fibers are thinly myelinated A δ fibers or unmyelinated C fibers with unencapsulated free nerve ending, with a small number of A β fibers associated with Pacinian corpuscles in the mesentery activation of visceral nociceptor are generally induced by ischemia, stretching of ligament attachments, spasm of smooth muscles, or distension of a hollow structure such as the gallbladder, common bile duct, or ureter. These stimuli usually occur in many visceral pathologic processes, and the pain they induce may serve a survival function by promoting immobility.

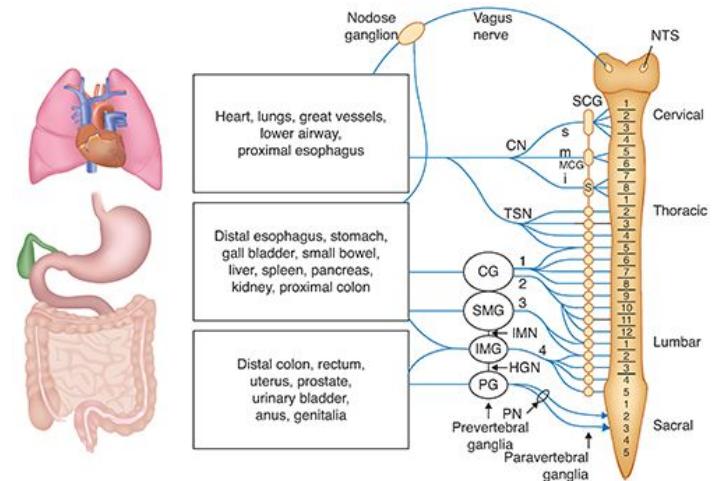


FIGURE 6.6 Visceral innervation. The vagus nerve, with cell bodies in the nodose ganglion and central terminals in the nucleus tractus solitarii (NTS), innervates organs in the thoracic and abdominal cavities. Afferent nerves with terminals in the spinal cord innervate the same thoracic and abdominal organs as well as those in the pelvic floor. Visceral spinal afferents pass through pre- and/or paravertebral ganglia en route to the spinal cord; their cell bodies are located in dorsal root ganglia, which are not illustrated. Abbreviations: CG, celiac ganglion; CN, cardiac nerves (i, inferior; m, middle; s, superior); HGN, hypogastric nerve; IMG, inferior mesenteric ganglia; IMN, intermesenteric nerve; MCG, middle cervical ganglia; PG, pelvic ganglion; PN, pelvic nerve; S, stellate ganglion; SCG, superior cervical ganglion; SMG, superior mesenteric ganglia; TSN, thoracic splanchnic nerves (1, greater; 2, lesser; 3, least; 4, lumbar splanchnic nerves). *Reprinted from McMahon SB, Koltzenburg M. Wall and Melzack's Textbook of Pain. 5th ed. Edinburgh: Churchill Livingstone; 2006. Figure 48.1. Copyright © 2006 Elsevier. With permission.*

Complex Regional Pain Syndromes

The IASP *Classification of Chronic Pain* defines complex regional pain syndrome (CRPS) as “a variety of painful conditions following injury which appears regionally having a distal predominance of abnormal findings, exceeding in both magnitude and duration the expected clinical course of the inciting event often resulting in significant impairment of motor function, and showing variable progression over time.” These chronic pain syndromes comprise different additional clinical features including spontaneous pain, allodynia, hyperalgesia, edema, autonomic abnormalities, active and passive movement disorders, and trophic changes of skin and subcutaneous tissues. Two types of CRPS, type I (reflex sympathetic dystrophy) and type II (causalgia), exist. The current IASP diagnostic clinical criteria for CRPS are as follows: *CRPS I* is (1) a syndrome that develops after an initiating noxious event; (2) spontaneous pain or allodynia/hyperalgesia occurs, is not limited to the territory of a single peripheral nerve, and is disproportionate to the inciting event; (3) there is or has been evidence of edema, skin blood flow abnormality, or abnormal sudomotor activity in the region of the pain since the inciting event; and (4) this diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction.

CRPS II (1) is a syndrome that develops after nerve injury. Spontaneous pain or allodynia/hyperalgesia occurs and is not necessarily limited to the territory of the injured nerve; (2) there is or has been evidence of edema, skin blood flow abnormality, or abnormal sudomotor activity in the region of the pain since the inciting event; and (3) this diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction.

CRPS I develops more often than CRPS II, and females are more often affected than males (2:1-4:1). The incidence of CRPS I is 1% to 2% after fractures, 12% after brain lesions, and of 5% after myocardial infarction, and the incidence of CRPS II in peripheral nerve injury varies from 2% to 14% in different series, with a mean around of 4%. The mechanism underlying the pathogenesis of CRPS remains unclear, although it is recognized that CRPS is a neurologic disease including the autonomic, sensory, and motor systems as

well as cortical areas involved in the processing of cognitive and affective information, and the inflammatory component (microglial activation) appears to be particularly important in the acute phase of the disease. So far, very few evidence-based treatment regimens for CRPS are available.

Pain in Neonate and Infant

The outdated thoughts that young children do not feel pain due to the immaturity of the PNS and CNS are no longer valid. Reflex responses to somatic stimuli begin at 15 days (E15, where gestation is 21.5 days) in the rat fetus, and the human fetuses probably obtain painful perception at around 23 to 26 weeks.^{39,40} Postnatal maturity of pain behavior develops quickly after birth. Usually, newborns and young children have significantly lower pain threshold and exaggerated pain responses compared to adults.⁴¹ Some clinical studies reveal the long-term effects of neonatal painful experience, which is affected by several confounding factors such as gestational age at birth, length of intensive care stay, intensity of the stimulus, and parenting style. Usually, the toddlers and adolescents with neonatal painful experience exhibit long-lasting hypersensitivity to painful stimuli. For example, the infants with neonatal circumcision had higher behavioral pain scores and cried longer during vaccination at 4 to 6 months old.⁴² These observations highlight the clinical importance of optimal management of pain in neonate and infant.

Embryologic Origin and Localization of Pain

The position in the spinal cord to which visceral afferent fibers pass for each organ depends on the segment (dermatome) of the body from which the organ developed embryologically. This explains the phenomenon of referred pain to a site distal from the tissue causing the pain (**Figure 6.7**). For example, the heart originates in the neck and upper thorax such that visceral afferents enter the spinal cord at C3 to C5. As a result, the referred pain of myocardial ischemia is to the neck and arm. The gallbladder originates from the ninth thoracic segment, so visceral afferents from the gallbladder enter the spinal cord at T9. Skeletal muscle spasm caused by damage in adjacent tissues may also be a cause of referred pain. For example, pain from the ureter can cause reflex spasm of the lumbar muscles.

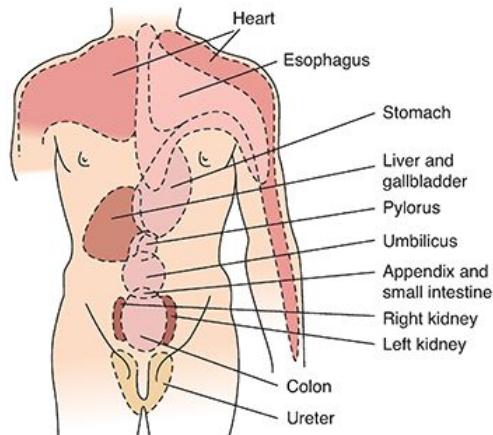


FIGURE 6.7 Surface area of referred pain from different visceral organs. Reprinted from Guyton AC, Hall JE. Textbook of Medical Physiology. 10th ed. Philadelphia, PA: W.B. Saunders; 2000. Copyright © 2000 Elsevier. With permission.

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Opioid Agonists and Antagonists

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Opioids are a cornerstone of modern perioperative care and pain management. The modern word “**opium**” is derived from the Greek word **opion** (“poppy juice”); the opium poppy (*Papaver somniferum*) is the source of 20 distinct alkaloids. Written mention of the medicinal use of poppy juice dates back to at least 300 BC, although religious use likely goes back much further.¹ Drugs derived from opium are referred to as **opiates**. Morphine, the best known opiate, was isolated in 1803, followed by codeine in 1832 and papaverine in 1848. Morphine can be synthesized, but it is more easily derived from opium. The term **narcotic** is derived from the Greek word for stupor and traditionally has been used to refer to potent morphine-like analgesics with the potential to produce physical dependence. The development of synthetic drugs with morphine-like properties has led to the use of the term **opioid** to refer to all exogenous substances, natural and synthetic, that bind specifically to any of several subpopulations of opioid receptors and produce at least some agonist (morphine-like) effects. Opioids are unique in producing analgesia without loss of touch, proprioception, or consciousness. A convenient classification of opioids includes opioid agonists, opioid agonist-antagonists, and opioid antagonists ([Table 7.1](#)).

TABLE 7.1		
Classification of opioid agonists and antagonists		
Agonists	Agonists-antagonists	Antagonists
Morphine	Pentazocine	Naloxone
Morphine-6-glucuronide	Butorphanol	Naltrexone
Meperidine	Nalbuphine	Nalmefene
Sufentanil	Buprenorphine	
Fentanyl	Nalorphine	
Alfentanil	Bremazocine	
Remifentanil	Dezocine	
Carfentanil	Meptazinol	
Codeine		
Hydromorphone		
Oxymorphone		
Oxycodone		
Hydrocodone		
Propoxyphene		
Methadone		
Tramadol		
Heroin (diacetylmorphine)		

Chemical Structure of Opium Alkaloids

The active components of opium can be divided into two distinct chemical classes: phenanthrenes and benzylisoquinolines. The principal phenanthrene alkaloids present in opium are morphine, codeine, and thebaine ([Figure 7.1](#)). The principal benzylisoquinoline alkaloids present in opium, which lack analgesic activity, are papaverine and noscapine.

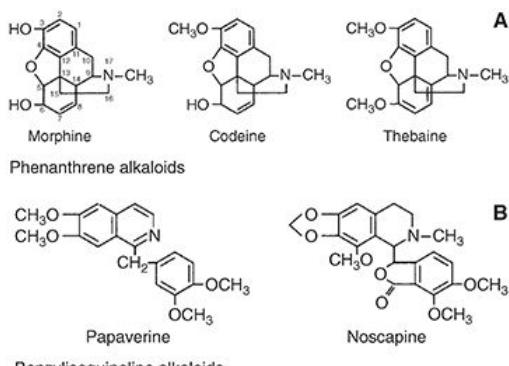


FIGURE 7.1 Chemical structures of opium alkaloids. Phenanthrene (A) and benzylisoquinoline (B) alkaloids.

The three rings of the phenanthrene core are composed of 14 carbon atoms. The fourth piperidine ring includes a tertiary amine nitrogen and is present in most opioid agonists. At pH 7.4, the tertiary amine nitrogen is highly ionized, making the molecule water soluble. These are chiral molecules, with levorotatory isomers being biologically active at opioid receptors.

Semisynthetic Opioids

Simple modification of the morphine molecule yields many derivative compounds with differing properties. For example, substitution of a methyl group for the hydroxyl group on carbon 3 results in methylmorphine (codeine). Substitution of acetyl groups on carbons 3 and 6 results in diacetylmorphine (heroin).

Hydromorphone has a carbonyl group instead of hydroxyl at position 6 and lacks a double bond between carbons 7 and 8. Thebaine has insignificant analgesic activity but serves as the precursor for etorphine (analgesic potency >1,000 times morphine).

Synthetic Opioids

Synthetic opioids contain the phenanthrene nucleus of morphine but are manufactured by synthesis rather than chemical modification of morphine. Morphine derivatives (levorphanol), methadone derivatives, benzomorphan derivatives (pentazocine), and phenylpiperidine derivatives (meperidine, fentanyl) are examples of groups of synthetic opioids. There are similarities in the molecular weights (236–326) and pK_as of phenylpiperidine derivatives and amide local anesthetics.

Fentanyl, sufentanil, alfentanil, and remifentanil ([Figure 7.2](#)) are synthetic opioids that are widely used to supplement general anesthesia or as primary anesthetic drugs in very high doses. There are important clinical differences between these opioids.^{2–4} The major pharmacodynamic differences between these drugs are potency and rate of equilibration between the plasma and the site of drug effect (biophase).

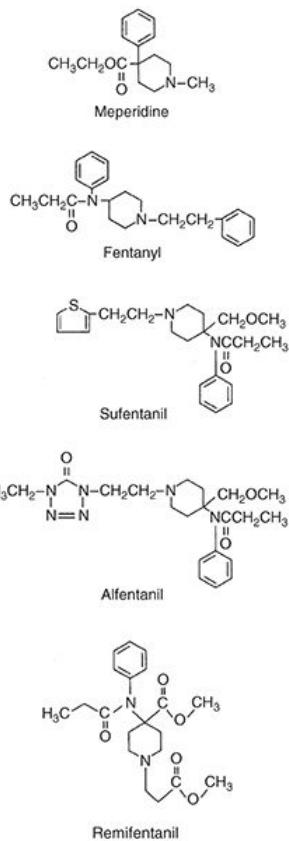


FIGURE 7.2 Synthetic opioid agonists.

Opioid Receptors

Opioid receptors are classified as μ , δ , and κ receptors (Table 7.2).^{5,6} The names of the three subtypes developed from the ligands originally found to bind to them or their tissue of origin (μ —morphine, κ —ketocyclazocine, δ —isolated from mouse *vas deferens*). These opioid receptors belong to a superfamily of seven transmembrane-segment guanine (G) protein-coupled receptors that includes muscarinic, adrenergic, and somatostatin receptors. The opioid receptors have been cloned, and their amino acid sequences defined.^{7,8} A single μ -receptor gene has been identified, and six distinct μ receptors have been identified.

TABLE 7.2

Classification of opioid receptors^a

	μ_1^b	μ_2^b	κ	δ
Effect	Analgesia (supraspinal, spinal)	Analgesia (spinal)	Analgesia (supraspinal, spinal)	Analgesia (supraspinal, spinal)
	Euphoria	Depression of ventilation	Dysphoria, sedation	Depression of ventilation
	Low abuse potential	Physical dependence	Low abuse potential	Physical dependence
	Miosis		Miosis	
		Constipation (marked)		Constipation (minimal)
	Bradycardia			
	Hypothermia			

	Urinary retention		Diuresis	Urinary retention
Agonists	Endorphins ^c	Endorphins ^c	Dynorphins	Enkephalins
	Morphine	Morphine		
	Synthetic opioids	Synthetic opioids		
Antagonists	Naloxone	Naloxone	Naloxone	Naloxone
	Naltrexone	Naltrexone	Naltrexone	Naltrexone
	Nalmefene	Nalmefene	Nalmefene	Nalmefene

^aAdapted from Atcheson R, Lambert DG. Update on opioid receptors. *Br J Anaesth.* 1994;73(2):132-134.

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^bThe existence of specific μ_1 and μ_2 receptors is not supported based on cloning studies of μ receptors.

^c μ Receptors seem to be a universal site of action for all endogenous opioid receptors.

In the brain, opioid receptors are primarily found in the periaqueductal gray, locus ceruleus, and the rostral ventral medulla. In the spinal cord, opioid receptors are found both on interneurons and primary afferent neurons in the dorsal horn. Consequently, direct application of opioid agonists to the spinal cord can produce intense analgesia.⁹ Outside the central nervous system (CNS), opioid receptors are found on sensory neurons and immune cells. For example, intraarticular morphine is known to produce analgesia after knee surgery, presumably through action on peripheral nerves.¹⁰ Immune cells recruited to sites of inflammation also secrete opioid peptides to provide local analgesia.¹¹ This may be useful in drug development. For example, lowering the pK_a of an opioid compound should cause its preferential activity at areas of reduced pH such as inflammation.¹²

μ -Opioid receptors are principally responsible for supraspinal and spinal analgesia. Theoretically, activation of a subpopulation of μ receptors (μ_1) is speculated to produce analgesia, whereas μ_2 receptors are responsible for hypoventilation, bradycardia, and physical dependence. Nevertheless, cloning of the μ receptors does not support the existence of separate μ_1 and μ_2 receptor subtypes.⁶ It is possible that such subtypes result from posttranslational modification of a common precursor protein. Additionally, the response of μ -opioid receptors to agonists can be significantly affected by β -arrestins, a family of proteins that regulate the activity of G protein-coupled receptors. For example, β -arrestins have been demonstrated to promote receptor desensitization (or resensitization) as well as to promote clathrin-mediated endocytosis.¹³ In principle, pharmacologic modulation of β -arrestin activity could improve the efficacy and tolerability of opioid agonists.¹⁴

Activation of κ receptors results in inhibition of neurotransmitter release via N-type calcium channels. Respiratory depression characteristic of μ -receptor activation is less prominent with κ -receptor activation, although dysphoria and diuresis may accompany activation of these receptors. A κ receptor-mediated analgesia may be less effective for high-intensity painful stimulation than μ opioid mediated. Opioid agonist-antagonists often act principally on κ receptors. The δ receptors respond to the endogenous ligands known as enkephalins, and these opioid receptors may serve to modulate the activity of the μ receptors.

Functional and physical interactions between these receptor subtypes have been noted.^{15,16} Heteromerization between μ - and δ -opioid receptors leads to distinct receptor pharmacology in that doses of δ -receptor ligands (agonists and antagonists) too low to trigger signaling can potentiate the binding and signaling of μ -receptor agonists. Chronic, but not acute, morphine treatment results in an increase in the μ - δ heteromers in key areas of the CNS that are implicated in pain processing.¹⁷

Previously considered opioid receptors, σ receptors (types 1 and 2) are widespread in the CNS and peripheral tissues. They are now known not to be true opioid receptors but have diverse roles in intracellular signaling, metabolic regulation, mitochondrial metabolism, and other functions.¹⁸

Endogenous Pain-Modulating Mechanisms

The logical reason for the existence of opioid receptors and endogenous opioid agonists is to function as an endogenous pain suppression system. Once pain is consciously perceived, it has served its purpose and it is

reasonable to posit that the ability to dampen this perception would have a survival benefit. Opioid receptors are located in areas of the brain (periaqueductal gray, locus ceruleus, and the rostral ventral medulla) and spinal cord (substantia gelatinosa) that are involved with pain perception, integration of pain impulses, and responses to pain (Figure 7.3).¹⁹ It is speculated that endorphins inhibit the release of excitatory neurotransmitters from terminals of nerves carrying nociceptive impulses. As a result, neurons are hyperpolarized, which suppresses spontaneous discharges and evoked responses. Analgesia induced by electrical stimulation of specific sites in the brain or mechanical stimulation of peripheral areas (acupuncture) most likely reflects release of endorphins.²⁰ Even the analgesic response to a placebo may also involve the release of endorphins. Sustained pain and stress induce the regional release of endogenous opioids interacting with μ -opioid receptors in a number of cortical and subcortical brain regions. The activation of the μ -opioid receptor system is associated with reductions in the sensory and affective ratings of the pain experience, with distinct neuroanatomical involvements.^{21,22}

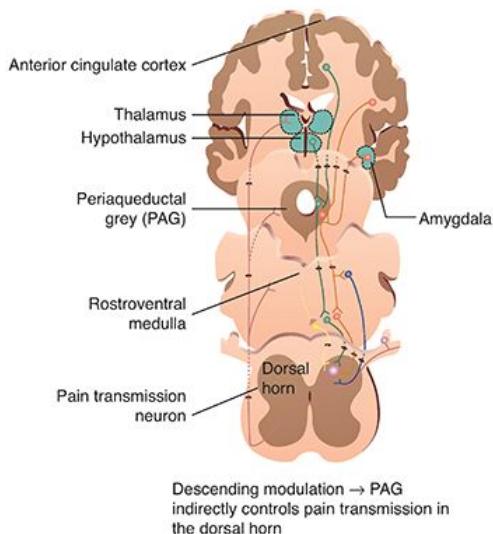


FIGURE 7.3 Opioid-sensitive pain modulation system. Limbic system areas project to the periaqueductal gray (PAG). The PAG in turn controls afferent pain transmission in the rostroventral medulla. This action can be both inhibitory (red) or facilitatory (green). *From Fields H. State-dependent opioid control of pain. Nat Rev Neurosci. 2004;5(7):565-575.*

In addition, one study demonstrated that positive treatment expectancy substantially enhanced (doubled) the analgesic benefit of remifentanil, whereas negative treatment expectancy abolished remifentanil analgesia.²³ These subjective effects were substantiated by significant changes in the neural activity in brain regions involved with the coding of pain intensity. The positive expectancy effects were associated with activity in the endogenous pain modulatory system, and the negative expectancy effects with activity in the hippocampus.²³ On the basis of subjective and objective evidence, we contend that an individual's expectation of a drug's effect critically influences its therapeutic efficacy and that regulatory brain mechanisms differ as a function of expectancy.

Common Opioid Side Effects

An ideal opioid agonist would have a high specificity for receptors, producing desirable responses (analgesia) and little or no specificity for receptors associated with side effects. To date, however, all opioids possess similar side effects that vary only in degree. Therefore, a focus on the effects of morphine provides a suitable starting point.

Cardiovascular System

Morphine, even in large doses, given to supine and normovolemic patients is unlikely to cause direct myocardial depression or hypotension. The same patients changing from a supine to a standing position, however, may manifest orthostatic hypotension and syncope, presumably reflecting morphine-induced impairment of compensatory sympathetic nervous system responses. For example, morphine decreases sympathetic nervous system tone to peripheral veins, resulting in venous pooling and subsequent decreases in venous return, cardiac output, and blood pressure.²⁴

Morphine can also evoke decreases in systemic blood pressure due to drug-induced bradycardia or histamine release. Morphine-induced bradycardia results from increased activity over the vagal nerves, which probably reflects stimulation of the vagal nuclei in the medulla. Morphine may also exert a direct depressant effect on the sinoatrial node and acts to slow conduction of cardiac impulses through the atrioventricular node. These actions, may, in part, explain decreased vulnerability to ventricular fibrillation in the presence of morphine. Administration of opioids (morphine) in the preoperative medication or before the induction of anesthesia (fentanyl) tends to slow heart rate during exposure to volatile anesthetics with or without surgical stimulation.²⁵

Opioid-induced histamine release and associated hypotension are variable in both incidence and severity. The magnitude of morphine-induced histamine release and subsequent decrease in systemic blood pressure can be minimized by (1) limiting the rate of morphine infusion to 5 mg/min intravenously (IV), (2) maintaining the patient in a supine to slightly head-down position, and (3) optimizing intravascular fluid volume. Conversely, administration of morphine, 1 mg/kg IV, over a 10-minute period produces substantial increases in the plasma concentrations of histamine that are paralleled by significant decreases in systemic blood pressure and systemic vascular resistance ([Figure 7.4](#)).²⁶ It is important to recognize, however, that not all patients respond to this rate of morphine infusion with the release of histamine, emphasizing the individual variability associated with the administration of this drug. In contrast to morphine, the infusion of fentanyl 50 µg/kg IV over a 10-minute period does not cause release of histamine in any patient (see [Figure 7.4](#)). Pretreatment of patients with H₁- and H₂-receptor antagonists does not alter release of histamine evoked by morphine but does prevent changes in systemic blood pressure and systemic vascular resistance.²⁷

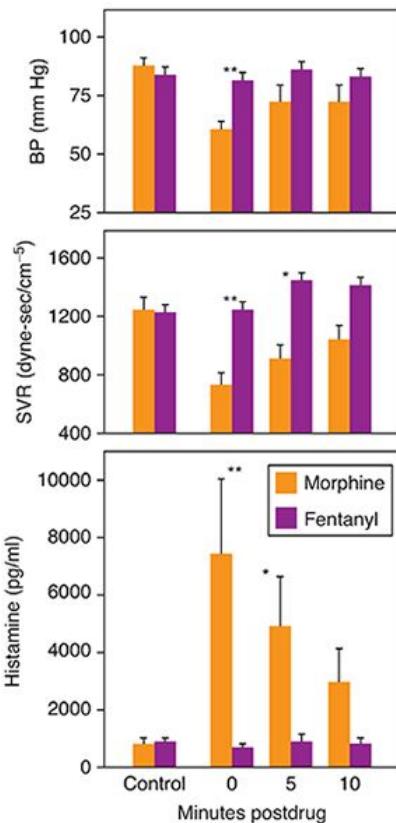


FIGURE 7.4 Morphine-induced decreases in systemic blood pressure (BP) and systemic vascular resistance (SVR) are accompanied by increases in the plasma concentration of histamine. Similar changes do not accompany the intravenous administration of fentanyl (* $P < .05$; ** $P < .005$; mean \pm standard error). *Reprinted with permission from Rosow CE, Moss J, Philbin DM, et al. Histamine release during morphine and fentanyl anesthesia. Anesthesiology. 1982;56(2):93-96. Copyright © 1982 American Society of Anesthesiologists, Inc.*

Morphine does not sensitize the heart to catecholamines or otherwise predispose to cardiac dysrhythmias as long as hypercarbia or arterial hypoxemia does not result from ventilatory depression. Tachycardia and hypertension that occur during anesthesia with morphine are not pharmacologic effects of the opioid but rather are responses to painful surgical stimulation that are not suppressed by morphine. Both the sympathetic nervous system and the renin-angiotensin axis contribute to these cardiovascular responses. Large doses of morphine or other opioid agonists may decrease the likelihood that tachycardia and hypertension will occur in response to painful stimulation, but once this response has occurred, administration of additional opioid is unlikely to be effective.

During anesthesia, however, opioids are commonly administered with inhaled or IV anesthetics to ensure amnesia. The combination of an opioid agonist such as morphine or fentanyl with nitrous oxide results in cardiovascular depression (decreased cardiac output and systemic blood pressure plus increased cardiac filling pressures), which does not occur when either drug is administered alone.²⁸ Likewise, decreases in systemic vascular resistance and systemic blood pressure may accompany the combination of an opioid and a benzodiazepine, whereas these effects do not accompany the administration of either drug alone ([Figure 7.5](#)).²⁹

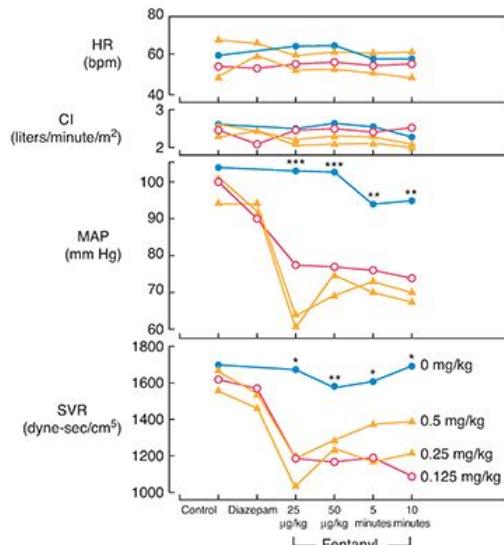


FIGURE 7.5 Administration of fentanyl (50 $\mu\text{g}/\text{kg}$ intravenously [IV] at 400 $\mu\text{g}/\text{minute}$) after injection of diazepam (0.125–0.50 mg/kg IV) is associated with significant decreases in mean arterial pressure (MAP) and systemic vascular resistance (SVR), whereas heart rate (HR) and cardiac index (CI) do not change. Administration of fentanyl in the absence of prior injection of diazepam (0 mg/kg) is devoid of circulatory effects. *Reprinted with permission from Tomicheck RC, Rosow CE, Philbin DM, et al. Diazepam-fentanyl interaction: hemodynamic and hormonal effects in coronary artery surgery. Anesth Analg. 1983;62(10):881–884. Copyright © 1983 International Anesthesia Research Society.*

Opioids have been increasingly recognized to play a role in protecting the myocardium from ischemia. Through several mechanisms, most prominently through σ and α receptors, opioids enhance the resistance of the myocardium to oxidative and ischemic stresses. Mitochondrial adenosine triphosphate-regulated potassium channels appear to be central to this signaling pathway.³⁰ Although once considered opioid receptors, σ receptors are now recognized to play diverse roles in cell signaling, metabolic regulation, and apoptosis and are not considered true opioid receptors.¹⁸

Ventilation

Because analgesic and ventilatory effects of opioids occur by similar mechanisms, it is assumed that equianalgesic doses of all opioids will produce some degree of ventilatory depression and reversal of ventilatory depression with an opioid antagonist always involves some reversal of analgesia. Opioid-induced depression of ventilation is characterized by decreased responsiveness of these ventilation centers to carbon dioxide as reflected by an increase in the resting arterial partial pressure of CO_2 and displacement of the carbon dioxide response curve to the right. Opioid agonists also interfere with pontine and medullary ventilatory centers that regulate the rhythm of breathing, leading to prolonged pauses between breaths and periodic breathing. It is possible that opioid agonists diminish sensitivity to carbon dioxide by decreasing the release of acetylcholine from neurons in the area of the medullary ventilatory center in response to hypercarbia. At the cellular level, there is evidence for β -arrestin mediation of opioid-induced ventilatory depression, which raises the possibility of using “biased ligands” at opioid receptors to mitigate this adverse effect.³¹

Depression of ventilation produced by opioid agonists is rapid and persists for several hours, as demonstrated by decreased ventilatory responses to carbon dioxide. High doses of opioids may result in apnea, but the patient remains conscious and able to initiate a breath if asked to do so. Death from an opioid overdose is almost invariably due to depression of ventilation.

Clinically, depression of ventilation produced by opioids manifests as a decreased frequency of breathing that is often accompanied by a compensatory increase in tidal volume. The incompleteness of this

compensatory increase in tidal volume is evidenced by predictable increases in the Paco_2 . Many factors influence the magnitude and duration of depression of ventilation produced by opioid agonists. For example, advanced age and the occurrence of natural sleep increase the ventilatory depressant effects of opioids. Conversely, pain from surgical stimulation counteracts depression of ventilation produced by opioids. Likewise, the analgesic effect of opioids slows breathing that has been rapid and shallow due to pain.

Opioids produce dose-dependent depression of ciliary activity in the airways. Increases in airway resistance after administration of an opioid are probably due to a direct effect on bronchial smooth muscle and an indirect action due to release of histamine (from some opioids).

Cough Suppression

Opioids depress cough by effects on the medullary cough centers that are distinct from the effects of opioids on ventilation. The greatest cough suppression occurs with opioids that have bulky substitutions at the number 3 carbon position (codeine). One useful property of dextrorotatory isomers (such as dextromethorphan) is that they can suppress cough but do not produce analgesia or depression of ventilation. They are not, however, devoid of abuse potential.³²

Central Nervous System

In the absence of hypoventilation, opioids decrease cerebral blood flow and possibly intracranial pressure (ICP). These drugs must be used with caution in patients with head injury because of their (1) associated effects on wakefulness, (2) production of miosis, and (3) depression of ventilation with associated increases in ICP if the Paco_2 becomes increased. Furthermore, head injury may impair the integrity of the blood-brain barrier, with resultant increased sensitivity to opioids.

The effect of morphine on the electroencephalogram (EEG) resembles changes associated with sleep. For example, there is replacement of rapid α waves by slower δ waves. Recording of the EEG fails to reveal any evidence of seizure activity after administration of large doses of opioids (see “[Fentanyl](#)” section). Opioids do not alter the responses to neuromuscular-blocking drugs. Skeletal muscle rigidity, especially of the thoracic and abdominal muscles, is common when large doses of opioid agonists are administered rapidly and IV.³³ Clonic skeletal muscle activity (myoclonus) occurring during administration of opioids may resemble grand mal seizures, but the EEG does not reflect seizure activity. Skeletal muscle rigidity may be related to actions at opioid receptors and involve interactions with dopaminergic and γ -aminobutyric acid-responsive neurons.

Miosis is due to an excitatory action of opioids on the autonomic nervous system component of the Edinger-Westphal nucleus of the oculomotor nerve. Tolerance to the miotic effect of morphine is not prominent. Miosis can be antagonized by atropine, and profound arterial hypoxemia in the presence of morphine can still result in mydriasis.

Rigidity

Rapid IV administration of large doses of an opioid (particularly fentanyl and its derivatives as used in cardiac surgery) can lead to generalized skeletal muscle rigidity. This can be severe enough to interfere with manual ventilation. Although generally termed “chest wall” rigidity, evidence supports the conclusion that the majority of resistance to ventilation is due to laryngeal musculature contraction. Inhibition of striatal release of γ -aminobutyric acid and increased dopamine production are the likely explanations for opioid-induced increased skeletal muscle tone.³⁴ The reported incidence of difficult ventilation after a moderate dose of sufentanil ranges from 84% to 100%.³⁵ Treatment is muscle relaxation with neuromuscular-blocking drugs or opioid antagonism with naloxone.

Sedation

Postoperative titration of morphine frequently induces sedation that precedes the onset of analgesia.³⁶ The usual recommendation for morphine titration includes a short interval between boluses (5-7 minutes) to allow evaluation of its clinical effect. Sedation occurs in up to 60% of patients during morphine titration and

represents a common reason to discontinue morphine titration for postoperative analgesia. The assumption that sleep occurs when pain is relieved is not necessarily accurate, and morphine-induced sedation should not be considered as an indicator of appropriate analgesia during IV morphine titration.

Biliary Tract

Opioids can cause spasm of biliary smooth muscle, resulting in increases in biliary pressure that may be associated with epigastric distress or biliary colic. This pain may be confused with angina pectoris. Naloxone will relieve pain caused by biliary spasm but not myocardial ischemia. Conversely, nitroglycerin will relieve pain due to either biliary spasm or myocardial ischemia. Equal analgesic doses of fentanyl, morphine, meperidine, and pentazocine increase common bile duct pressure 99%, 53%, 61%, and 15% above predrug levels, respectively.³⁷ During surgery, opioid-induced spasm of the sphincter of Oddi may appear radiologically as a sharp constriction at the distal end of the common bile duct and be misinterpreted as a common bile duct stone. It may be necessary to reverse opioid-induced biliary smooth muscle spasm with naloxone so as to correctly interpret the cholangiogram. Glucagon, 2 mg IV, also reverses opioid-induced biliary smooth muscle spasm and, unlike naloxone, does not antagonize the analgesic effects of the opioid.³⁸ However, biliary muscle spasm does not occur in most patients who receive opioids. Indeed, the incidence of spasm of the sphincter of Oddi is about 3% in patients receiving fentanyl as a supplement to inhaled anesthetics.³⁹

Contraction of the smooth muscles of the pancreatic ducts is probably responsible for increases in plasma amylase and lipase concentrations that may be present after the administration of morphine. Such increases may confuse the diagnosis when acute pancreatitis is a possibility.

Gastrointestinal Tract

Commonly used opioids such as morphine, meperidine, and fentanyl can produce spasm of the gastrointestinal smooth muscles, resulting in a variety of side effects including constipation, biliary colic, and delayed gastric emptying.

Morphine decreases the propulsive peristaltic contractions of the small and large intestines and enhances the tone of the pyloric sphincter, ileocecal valve, and anal sphincter. The delayed passage of intestinal contents through the colon allows increased absorption of water. As a result, constipation often accompanies therapy with opioids and may become a debilitating problem in patients who require chronic opioid therapy, as little tolerance develops to this effect. Of interest, opium was used to treat diarrhea before its use as an analgesic was popularized.

Increased biliary pressure occurs when the gallbladder contracts against a closed or narrowed sphincter of Oddi. Passage of gastric contents into the proximal duodenum is delayed because there is increased tone at the gastroduodenal junction. In this regard, preoperative medication that includes an opioid could slow gastric emptying (potentially increase the risk of aspiration) or delay the absorption of orally administered drugs. All these effects may be reversed or prevented by a peripheral-acting opioid antagonist (see “[Opioid Antagonists](#)” section).

Nausea and Vomiting

Opioid-induced nausea and vomiting are caused by direct stimulation of the chemoreceptor trigger zone in the floor of the fourth ventricle. This may reflect the role of opioid agonists as partial dopamine agonists at dopamine receptors in the chemoreceptor trigger zone. Indeed, apomorphine is a profound emetic and is also the most potent of the opioids at dopamine receptors. Stimulation of dopamine receptors as a mechanism for opioid-induced nausea and vomiting is consistent with the antiemetic efficacy of butyrophenones and phenothiazines. Morphine may also cause nausea and vomiting by increasing gastrointestinal secretions and delaying passage of intestinal contents toward the colon. Nausea and vomiting are relatively uncommon in recumbent patients given morphine, suggesting that a vestibular component may also contribute to opioid-induced nausea and vomiting.

Genitourinary System

Morphine can increase the tone and peristaltic activity of the ureter. In contrast to similar effects on biliary tract smooth muscle, the same opioid-induced effects on the ureter can be reversed by an anticholinergic drug such as atropine. Urinary urgency is produced by opioid-induced augmentation of detrusor muscle tone, but, at the same time, the tone of the urinary sphincter is enhanced, making voiding difficult.

Antidiuresis that accompanies administration of morphine to animals has been attributed to opioid-induced release of arginine vasopressin hormone (antidiuretic hormone). In humans, however, administration of morphine in the absence of painful surgical stimulation does not evoke the release of this hormone.⁴⁰ Furthermore, when morphine is administered in the presence of an adequate intravascular fluid volume, there is no change in urine output.

Cutaneous Changes

Morphine causes cutaneous blood vessels to dilate. The skin of the face, neck, and upper chest frequently becomes flushed and warm. These changes in cutaneous circulation are in part caused by the release of histamine. Histamine release probably accounts for urticaria and erythema commonly seen at the morphine injection site. In addition, morphine-induced histamine release probably accounts for conjunctival erythema and pruritus. Localized cutaneous evidence of histamine release, especially along the vein into which morphine is injected, does not represent an allergic reaction.

Placental Transfer

Opioids are readily transported across the placenta.⁴¹ Therefore, depression of the neonate can occur as a consequence of administration of opioids to the mother during labor. However, their effects on neonates are quite variable: Maternal administration of morphine may produce greater neonatal depression than meperidine.⁴² Although fentanyl crosses the placenta, it does not produce significant neonatal depression unless large doses are used. Chronic maternal use of an opioid can result in the development of physical dependence in the fetus. Subsequent administration of naloxone to the neonate can precipitate a life-threatening neonatal withdrawal syndrome.

Drug Interactions

The ventilatory depressant effects of some opioids may be exaggerated by amphetamines, phenothiazines, monoamine oxidase inhibitors, and tricyclic antidepressants. For example, patients receiving monoamine oxidase inhibitors may experience exaggerated CNS depression and hyperpyrexia after administration of an opioid agonist, especially meperidine.⁴³

Hormonal Changes

Prolonged opioid therapy may influence the hypothalamic-pituitary-adrenal axis and the hypothalamic-pituitary-gonadal axis, leading to endocrine and immune effects.^{44,45} Morphine may cause a progressive decrease in plasma cortisol concentrations. The main effects of opioids on the hypothalamic-pituitary-gonadal axis involve modulation of hormone release including increased prolactin and decreased luteinizing hormone, follicle-stimulating hormone, testosterone, and estrogen concentrations.

Overdose

The principal manifestation of opioid overdose is depression of ventilation manifesting as a slow breathing frequency, which may progress to apnea. Pupils are symmetric and miotic unless severe arterial hypoxemia is present, which results in mydriasis. Skeletal muscles are flaccid, and upper airway obstruction may occur. Pulmonary edema commonly occurs, but the mechanism is not known. Hypotension and seizures develop if arterial hypoxemia persists. The triad of miosis, hypoventilation, and coma should suggest overdose with an opioid. Treatment of opioid overdose is mechanical ventilation of the patient's lungs with oxygen and administration of an opioid antagonist such as naloxone. Administration of an opioid antagonist to treat opioid overdose may precipitate acute withdrawal in dependent patients. With the recent increase in opioid-overdose deaths, the availability of intranasal or intramuscular (IM) naloxone for out-of-hospital treatment is critical. For patients being prescribed high-dose opioids, a prescription for naloxone as a rescue drug is

appropriate. Extremely high doses of naloxone may be necessary for individuals using ultra-potent opioids such as carfentanil.

Provocation of Coughing

Paradoxically, preinduction administration of fentanyl, sufentanil, or alfentanil may be associated with significant reflex coughing.⁴⁶ The exact cause of opioid-induced cough is unclear but is thought to be due to imbalance between sympathetic and vagal innervation of the airways and/or stimulation of juxtapacillary irritant receptors.⁴⁷ Morphine and hydromorphone do not appear to cause this reaction.

Pharmacodynamic Tolerance and Physical Dependence

Pharmacodynamic tolerance and physical dependence with repeated opioid administration are characteristics of all opioid agonists and are among the major limitations of their clinical use. Cross-tolerance develops between all the opioids, although incomplete, as manifested by the reduced doses required with opioid rotation. Tolerance can occur without physical dependence, but the reverse does not seem to occur.

Tolerance is the development of the requirement for increased doses of a drug (in this case, an opioid agonist) to achieve the same effect previously achieved with a lower dose. Such acquired tolerance usually takes 2 to 3 weeks to develop with analgesic doses of morphine, although acute tolerance can develop much more quickly with highly potent opioids.⁴⁸ Tolerance develops to analgesic, euphoric, sedative, depression of ventilation, and emetic effects of opioids but not to their effects on miosis and bowel motility. The potential for physical dependence depends on the agonist effect of opioids. Indeed, physical dependence does not occur with opioid antagonists and is less likely with opioid agonist-antagonists. When opioid agonist actions predominate, there often develops, with repeated use, both psychological and physiologic need for the drug.

Physical dependence on morphine usually requires about 25 days to develop. Some degree of physical dependence, however, occurs after only 48 hours of continuous medication. When physical dependence is established, discontinuation of the opioid agonist produces a withdrawal abstinence syndrome that may vary depending on individual and environmental factors (**Table 7.3**).⁴⁹ Initial symptoms of withdrawal include yawning, diaphoresis, lacrimation, or coryza. Insomnia and restlessness are prominent. Abdominal cramps, nausea, vomiting, and diarrhea reach their peak in 72 hours and then decline over the next 7 to 10 days. During withdrawal, tolerance to morphine is rapidly lost, and the syndrome can be terminated by a modest dose of opioid agonist. The longer the period of abstinence, the smaller the dose of opioid agonist that will be required.

TABLE 7.3

Time course of opioid withdrawal^a

Opioid	Onset	Peak intensity	Duration
Meperidine	2-6 hours	6-12 hours	4-5 days
Fentanyl	2-6 hours	6-12 hours	4-5 days
Morphine	6-18 hours	36-72 hours	7-10 days
Heroin	6-18 hours	36-72 hours	7-10 days
Methadone	24-48 hours	3-21 days	6-7 weeks

^aAdapted from Mitra S, Sinatra RS. Perioperative management of acute pain in the opioid-dependent patient. *Anesthesiology*. 2004;101(1):212-227.

Pharmacodynamic tolerance has been related to neurologic changes that take place after long-term exposure to the opioid.⁴⁹ The classic explanation for tolerance to a receptor agonist involved changes occurring at the level of the receptors and involve receptor desensitization. Opioid receptors on the cell membrane surfaces become gradually desensitized by reduced transcription and subsequent decreases in the absolute numbers of opioid receptors (downregulation). A second mechanism proposed to explain pharmacodynamic tolerance involves upregulation of the cyclic adenosine monophosphate (cAMP) system. Acutely, opioids inhibit functional activity of cAMP pathways by blocking adenylate cyclase, the enzyme that

catalyzes the synthesis of cAMP. Long-term opioid exposure is associated with gradual recovery of cAMP pathways, and tolerance develops. Increased synthesis of cAMP may be responsible for physical dependence and physiologic changes associated with withdrawal. Upregulation of cAMP has been most clearly demonstrated in the locus ceruleus of the brain. Clonidine, a centrally acting α_2 -adrenergic agonist that diminishes transmission in sympathetic pathways in the CNS, is an effective drug in suppressing withdrawal signs in persons who are physically dependent on opioids. Tolerance is not due to enzyme induction because no increase in the rate of metabolism of opioid agonists occurs.

Long-term pharmacodynamic tolerance characterized by opioid insensitivity may persist for months or years in some individuals and most likely represents persistent neural adaptation.⁴⁹ In this regard, *N*-methyl-D-aspartate (NMDA) glutamate receptors are important in the development of opioid tolerance and increased pain sensitivity. Prolonged exposure to opioids activates NMDA receptors via second messenger mechanisms and also downregulates spinal glutamate transporters. The resultant high synaptic concentrations of glutamate and NMDA receptor activation contribute to opioid tolerance and abnormal pain sensitivity (pronociceptive or sensitization process). The observation that treatment with small doses of ketamine (an NMDA receptor antagonist) abolishes the acute opioid tolerance seen with remifentanil supports this hypothesis.⁵⁰

Opioid Agonists

Opioid agonists include but are not limited to morphine, meperidine, fentanyl, sufentanil, alfentanil, and remifentanil (see [Table 7.1](#)).⁵¹ The most notable feature of the clinical use of opioids is the extraordinary variation in dose requirements for pain management.⁵² This interindividual variation emphasizes that usual doses of opioids may produce inadequate or excessive opioid effects. Opioid rotation may be useful when dose escalation is not effective in treating pain.

Morphine

Isolated in 1806 and named for the Greek god of dreams, morphine is the prototype opioid agonist to which all other opioids are compared. In humans, morphine produces analgesia, euphoria, sedation, and a diminished ability to concentrate. Other sensations include nausea, a feeling of body warmth, heaviness of the extremities, dryness of the mouth, and pruritus, especially in the cutaneous areas around the nose. The cause of pain persists, but even low doses of morphine increase the threshold to pain and modify the perception of noxious stimulation such that it is no longer experienced as pain. Continuous, dull pain is relieved by morphine more effectively than is sharp, intermittent pain. Analgesia is most prominent when morphine is administered before the painful stimulus occurs.⁵³

Pharmacokinetics

Morphine is well absorbed after IM administration, with onset of effect in 15 to 30 minutes and a peak effect in 45 to 90 minutes. The clinical duration of action is about 4 hours. Morphine can be administered orally for treatment of chronic pain recognizing that absorption from the gastrointestinal tract may be limited. Morphine is usually administered IV in the perioperative period, thus eliminating the unpredictable influence of drug absorption. The peak effect (equilibration time between the blood and brain) after IV administration of morphine is delayed compared with opioids such as fentanyl and alfentanil, requiring about 15 to 30 minutes ([Table 7.4](#)). Morphine inhaled as an aerosol from a nebulizer may act on afferent nerve pathways in the airways to relieve dyspnea as associated with lung cancer and associated pleural effusion.⁵⁴ However, profound depression of ventilation may follow aerosol administration of morphine.⁵⁵ The onset and duration of the analgesic effects of morphine are similar after IV administration or inhalation via a pulmonary drug delivery system that produces a fine aerosol.⁵⁶

TABLE 7.4

Pharmacokinetics of opioid agonists

pK Percent nonionized (pH 7.4)	Protein binding (%)	Clearance (mL/minute)	Volume of distribution (L)	Partition coefficient	Elimination half-time (hour)	Context-sensitive half- time: 4-hour infusion (minute)	Effect-site (blood/brain)
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									equilibration time (minute)
Morphine	7.9	23	35	1,050	224	1	1.7-3.3		
Meperidine	8.5	7	70	1,020	305	32	3-5		
Fentanyl	8.4	8.5	84	1,530	335	955	3.1-6.6	260	6.8
Sufentanil	8.0	20	93	900	123	1,727	2.2-4.6	30	6.2
Alfentanil	6.5	89	92	238	27	129	1.4-1.5	60	1.4
Remifentanil	7.3	58	66-93	4,000	30		0.17-0.33	4	1.1

Plasma morphine concentrations after rapid IV injections do not correlate closely with the drug's pharmacologic activity, likely due to the delay in transit of morphine across the blood–brain barrier. Cerebrospinal fluid (CSF) concentrations of morphine peak 15 to 30 minutes after IV injection and decay more slowly than plasma concentrations (**Figure 7.6**).⁵⁷ As a result, the analgesic and ventilatory depressant effects of morphine may not be evident during the initial high plasma concentrations after IV administration of the opioid. Likewise, these same drug effects persist despite decreasing plasma concentrations of morphine. Moderate analgesia probably requires maintenance of plasma morphine concentrations of at least 0.05 µg/mL.⁵⁸

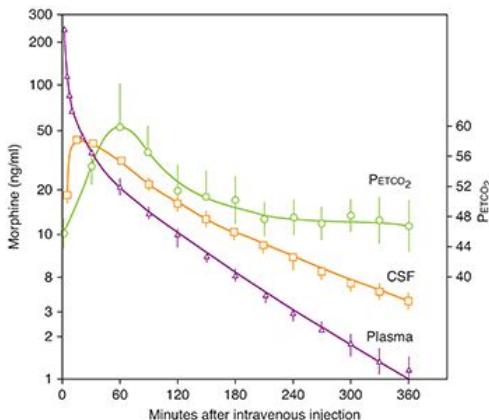


FIGURE 7.6 Cerebrospinal fluid (CSF) concentrations following intravenous administration of morphine decay more slowly than plasma concentrations. The end-tidal CO₂ concentration (PETCO₂) remains increased despite a decreasing plasma concentration of morphine (mean ± standard error). Reprinted with permission from Murphy MR, Hug CC Jr. Pharmacokinetics of intravenous morphine in patients anesthetized with enflurane-nitrous oxide. Anesthesiology. 1981;54(3):187-192. Copyright © 1981 American Society of Anesthesiologists, Inc.

Only a small amount of administered morphine gains access to the CNS. For example, it is estimated that <0.1% of morphine that is administered IV has entered the CNS at the time of peak plasma concentrations. Reasons for poor penetration of morphine into the CNS include (1) relatively poor lipid solubility, (2) high degree of ionization at physiologic pH, (3) protein binding, and (4) rapid conjugation with glucuronic acid. Alkalization of the blood, as produced by hyperventilation of the patient's lungs, will increase the nonionized fraction of morphine and thus enhance its passage into the CNS. Nevertheless, respiratory acidosis, which decreases the nonionized fraction of morphine, results in higher plasma and brain concentrations of morphine than are present during normocarbia (**Figure 7.7**).⁵⁹ This suggests that carbon dioxide–induced increases in cerebral blood flow and enhanced delivery of morphine to the brain are more important than the fraction of drug that exists in either the ionized or nonionized fraction. In contrast to the CNS, morphine accumulates rapidly in the kidneys, liver, and skeletal muscles. Morphine, unlike fentanyl, does not undergo significant first-pass uptake into the lungs.⁶⁰

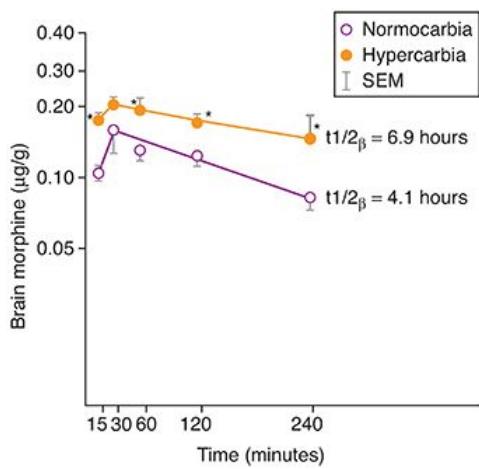


FIGURE 7.7 Hypercarbia, which decreases the nonionized fraction of morphine, results in a higher brain concentration and longer elimination half-time ($t_{1/2\beta}$) than occurs in the presence of normocarbia (* $P < .05$). Abbreviation: SEM, standard error of the measurement. *Reprinted with permission from Finck AD, Ngai SH, Berkowitz BA. Antagonism of general anesthesia by naloxone in the rat. Anesthesiology. 1977;46(4):241-245. Copyright © 1977 American Society of Anesthesiologists, Inc.*

Metabolism

Metabolism of morphine is primarily conjugation with glucuronic acid in hepatic and extrahepatic sites, especially the kidneys. About 75% to 85% of a dose of morphine appears as morphine-3-glucuronide, and 5% to 10% as morphine-6-glucuronide (a ratio of 9:1). Morphine-3-glucuronide is detectable in the plasma within 1 minute after IV injection, and its concentration exceeds that of unchanged drug by almost 10-fold within 90 minutes (Figure 7.8).⁵⁷ An estimated 5% of morphine is demethylated to normorphine, and a small amount of codeine (methylmorphine) may also be formed. Metabolites of morphine are eliminated principally in the urine, with only 7% to 10% undergoing biliary excretion. Morphine-3-glucuronide is detectable in the urine for up to 72 hours after the administration of morphine. A small fraction (1%-2%) of injected morphine is recovered unchanged in the urine.

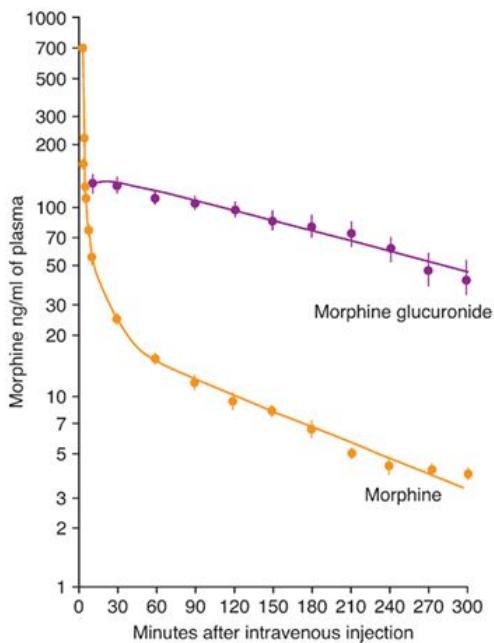


FIGURE 7.8 Morphine glucuronide is detectable in the plasma within 1 minute after intravenous injection, and its concentration exceeds that of unchanged morphine by almost 10-fold within 90 minutes (mean \pm standard error). Reprinted with permission from Murphy MR, Hug CC Jr. Pharmacokinetics of intravenous morphine in patients anesthetized with enflurane-nitrous oxide. *Anesthesiology*. 1981;54(3):187-192. Copyright © 1981 American Society of Anesthesiologists, Inc.

Morphine-3-glucuronide is pharmacologically inactive, whereas morphine-6-glucuronide produces analgesia and depression of ventilation via its agonist actions at μ receptors.⁶¹ In fact, the ventilatory response to carbon dioxide is impacted similarly by morphine and morphine-6-glucuronide (Figure 7.9).⁶² The duration of action of morphine-6-glucuronide is greater than that of morphine, and it is possible that the majority of analgesic activity attributed to morphine is actually due to morphine-6-glucuronide, especially with long-term administration of morphine.⁶³ Morphine and morphine-6-glucuronide bind to μ -opioid receptors with comparable affinity, whereas the analgesic potency of morphine-6-glucuronide is 650-fold higher than morphine.⁶⁴

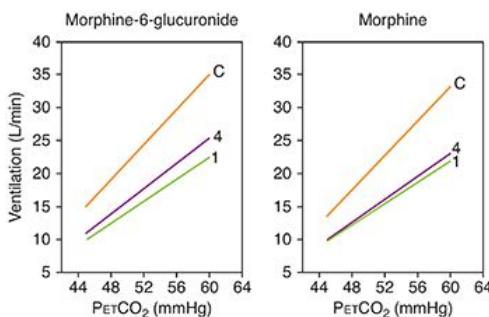


FIGURE 7.9 Influence of 0.2 mg/kg morphine-6-glucuronide intravenously (IV) and 0.13 mg/kg morphine IV on the ventilatory response to carbon dioxide. The effects of both opioids were similar over the 4-hour period of study. Abbreviation: PETCO₂, end-tidal PCO₂. Reprinted with permission from Romberg R, Olofson E, Satron E, et al. Pharmacodynamic effect of morphine-6-glucuronide versus morphine on hypoxic and hypercapnic breathing in healthy volunteers. *Anesthesiology*. 2003;99(4):788-798. Copyright © 2003 American Society of Anesthesiologists, Inc.

Renal metabolism makes a significant contribution to the total metabolism of morphine, which offers a possible explanation for the absence of any decrease in systemic clearance of morphine in patients with hepatic cirrhosis or during the anhepatic phase of orthotopic liver transplantation.⁶⁵

Elimination of morphine glucuronides may be impaired in patients with renal failure, causing an accumulation of metabolites and unexpected ventilatory depressant effects of small doses of opioids (Figure 7.10).⁶⁶ Indeed, prolonged depression of ventilation (<7 days) has been observed in patients in renal failure after administration of morphine.⁶⁷ Formation of glucuronide conjugates may be impaired by monoamine oxidase inhibitors, which is consistent with exaggerated effects of morphine when administered to patients being treated with these drugs.

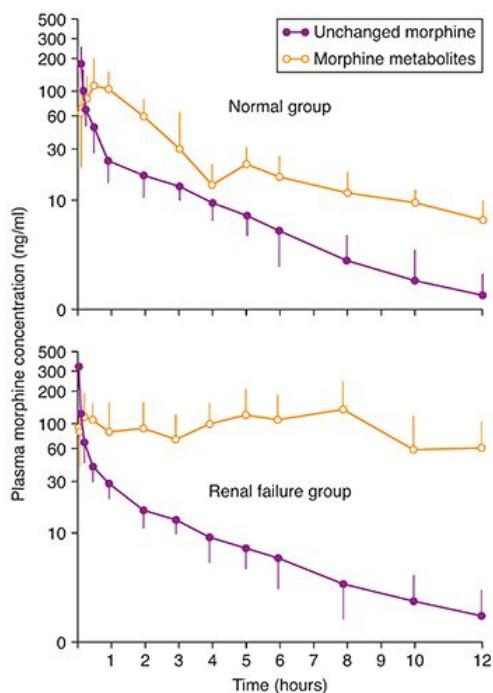


FIGURE 7.10 Plasma concentrations of unchanged morphine (closed circles) and morphine metabolites (open circles) in normal and renal failure patients. Reprinted with permission from Chauvin M, Sandouk P, Scherrmann JM, et al. Morphine pharmacokinetics in renal failure. *Anesthesiology*. 1987;66(3):327-331. Copyright © 1987 American Society of Anesthesiologists, Inc.

Elimination Half-Time

After IV administration of morphine, the elimination of morphine-3-glucuronide is somewhat longer than for morphine (see [Table 7.4](#) and [Figure 7.8](#)).⁵⁷ The decrease in the plasma concentration of morphine after initial distribution of the drug is principally due to metabolism because only a small amount of unchanged opioid is excreted in the urine. Plasma morphine concentrations are higher in the elderly than in young adults ([Figure 7.11](#)).⁵⁸ In the first 4 days of life, the clearance of morphine is decreased and its elimination half-time is prolonged compared with that found in older infants.⁶⁸ This is consistent with the observation that neonates are more sensitive than older children to the respiratory depressant effects of morphine. Patients with renal failure exhibit higher plasma and CSF concentrations of morphine and morphine metabolites than do normal patients, reflecting a smaller volume of distribution (Vd).⁶⁹ Possible accumulation of morphine-6-glucuronide suggests the need for caution when administering morphine to patients with significant renal dysfunction. Concentrations of morphine in colostrum of parturients receiving patient-controlled analgesia (PCA) with morphine are low, and it is unlikely that significant amounts of drug will be transferred to the breast-fed neonate.⁷⁰

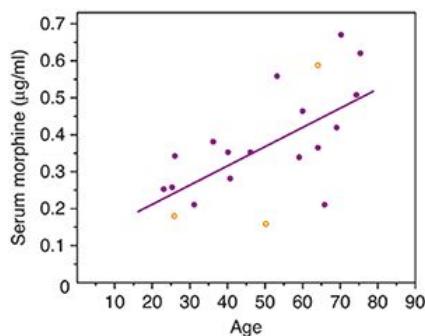


FIGURE 7.11 The plasma (serum) concentration of morphine increases progressively with advancing age. From Berkowitz BA, Ngai SH, Yang JC, et al. *The disposition of morphine in surgical patients*. Clin Pharmacol Ther. 1975;17(6):629-635. Copyright © 1975 American Society for Clinical Pharmacology and Therapeutics. Reprinted by permission of John Wiley & Sons, Inc.

Sex

Sex may affect opioid analgesia, but the direction and magnitude of these differences depend on many interacting variables including the opioid used.⁷¹ Morphine exhibits greater analgesic potency and slower speed of offset in women than men.⁷² This observation is consistent with higher postoperative opioid consumption in men compared with women. Morphine has also been demonstrated to cause greater respiratory depression in women.⁷³ Making broad assertions about the clinical significance of these differences is difficult because pain perception, opioid-related side effects, and sensitivity to opioids all affect opioid dosing requirements and may lead to differences in some contexts but not others.⁷⁴

Side Effects

Side effects described for morphine are also characteristic of other opioid agonists, although the incidence and magnitude may vary.

Meperidine

First synthesized in 1939, meperidine (also referred to as **pethidine**) is a synthetic opioid agonist at μ - and α -opioid receptors and is derived from phenylpiperidine (see [Figure 7.1](#)). There are several analogues of meperidine, including fentanyl, sufentanil, alfentanil, and remifentanil. Meperidine shares several structural features that are present in local anesthetics including a tertiary amine, an ester group, and a lipophilic phenyl group. Indeed, meperidine administered intrathecally blocks sodium channels to a degree comparable with lidocaine and can be used to provide surgical anesthesia.⁷⁵ Structurally, meperidine is similar to atropine, and it possesses a mild atropine-like antispasmodic effect on smooth muscle.

Pharmacokinetics

Meperidine is about one-tenth as potent as morphine. The duration of action of meperidine is 2 to 4 hours, making it a shorter acting opioid agonist than morphine. In equal analgesic doses, meperidine produces equivalent sedation, euphoria, nausea, vomiting, and depression of ventilation to morphine. Meperidine is absorbed from the gastrointestinal tract, but extensive first-pass hepatic metabolism (up to 80%) limits its oral usefulness.

Metabolism

Hepatic metabolism of meperidine is extensive, with about 90% of the drug initially undergoing demethylation to normeperidine and hydrolysis to meperidinic acid.⁷⁶ Normeperidine subsequently undergoes hydrolysis to normeperidinic acid. Urinary excretion is the principal elimination route and is pH dependent. For example, if the urinary pH is <5, as much as 25% of meperidine is excreted unchanged. Indeed, acidification of the urine can be considered in an attempt to speed elimination of meperidine. Decreased renal function can predispose to accumulation of normeperidine.

Normeperidine has an elimination half-time of 15 hours (35 hours in patients in renal failure) and can be detected in urine for as long as 3 days after administration of meperidine. This metabolite is about one-half as active as meperidine as an analgesic. In addition, normeperidine produces CNS stimulation. Normeperidine toxicity manifesting as myoclonus and seizures is most likely during prolonged administration of meperidine as during PCA, especially in the presence of impaired renal function.⁷⁶ Normeperidine may also be important in meperidine-induced delirium (confusion, hallucinations), which has been observed in patients receiving the drug for longer than 3 days, corresponding to accumulation of this active metabolite.

Elimination Half-Time

The elimination half-time of meperidine is 3 to 5 hours (see [Table 7.4](#)). Because clearance of meperidine primarily depends on hepatic metabolism, it is possible that large doses of opioid would saturate enzyme systems and result in prolonged elimination half-times. Nevertheless, elimination half-time is not altered by doses of meperidine up to 5 mg/kg IV. About 60% of meperidine is bound to plasma proteins. Elderly patients manifest decreased plasma protein binding of meperidine, resulting in increased plasma concentrations of free drug and an apparent increased sensitivity to the opioid. The increased tolerance of alcoholics to meperidine and other opioids presumably reflects an increased Vd, resulting in lower plasma concentrations of meperidine for a given dose.

Clinical Uses

The clinical use of meperidine has declined greatly in recent years. Meperidine is the only opioid considered adequate for surgery when administered intrathecally.⁷⁷ An IM injection of meperidine for postoperative analgesia results in peak plasma concentrations that vary three- to fivefold as well as a time required to achieve peak concentrations that varies three- to sevenfold among patients.⁷⁸ The minimum analgesic plasma concentration of meperidine is highly variable among patients; however, in the same patient, differences in concentrations as small as 0.05 µg/mL can represent a margin between no relief and complete analgesia. A plasma meperidine concentration of 0.7 µg/mL would be expected to provide postoperative analgesia in about 95% of patients.⁷⁹ Normeperidine toxicity has been described in patients receiving meperidine for PCA.⁷⁶ Therefore, because there are other effective agents, PCA with meperidine cannot be recommended.

Meperidine may be effective in suppressing postoperative shivering that may result in detrimental increases in metabolic oxygen consumption. The antishivering effects of meperidine may reflect stimulation of α receptors (estimated to represent 10% of its activity) and a drug-induced decrease in the shivering threshold (not present with alfentanil, clonidine, propofol, or volatile anesthetics).⁸⁰⁻⁸² In addition, meperidine is a potent agonist at α_2 -adrenergic receptors, which might contribute to antishivering effects.⁸³ Indeed, clonidine is even more effective than meperidine in reducing postoperative shivering. Butorphanol (a α -receptor agonist-antagonist) stops shivering more effectively than opioids with a predominant μ -opioid receptor agonist effect. Evidence for a role of α receptors in the antishivering effects of meperidine and butorphanol is the failure of naloxone to completely inhibit this drug-induced effect.

Unlike morphine, meperidine is not useful for the treatment of diarrhea and is not an effective cough suppressant. Meperidine is not used in high doses because of significant negative cardiac inotropic effects plus histamine release in a substantial number of patients.⁸⁴

Side Effects

The side effects of meperidine generally resemble those described for morphine. Meperidine, in contrast to morphine, rarely causes bradycardia but instead may increase heart rate, reflecting its modest atropine-like qualities. Large doses of meperidine result in decreases in myocardial contractility, which, among opioids, is unique for this drug. Delirium and seizures, when they occur, presumably reflect accumulation of normeperidine, which has stimulating effects on the CNS.

Serotonin syndrome (autonomic instability with hypertension, tachycardia, diaphoresis, hyperthermia, behavioral changes including confusion and agitation, and neuromuscular changes manifesting as hyperreflexia) occurs when drugs capable of increasing serotonin administration are administered. In severe cases, coma, seizures, coagulopathy, and metabolic acidosis may develop. Administration of meperidine to patients receiving antidepressant drugs (monoamine oxidase inhibitors, fluoxetine) may elicit this syndrome.⁸⁵

Meperidine readily impairs ventilation and may be even more of a ventilatory depressant than morphine. This opioid promptly crosses the placenta, and concentrations of meperidine in umbilical cord blood at birth may exceed maternal plasma concentrations.⁴² After equal analgesic doses, biliary tract spasm is less after meperidine injection than after morphine injection but greater than that caused by codeine.³⁷ Meperidine does not cause miosis but rather tends to cause mydriasis, reflecting its modest atropine-like actions. A dry mouth and an increase in heart rate are further evidence of the atropine-like effects of meperidine. Transient

neurologic symptoms have been described following the administration of intrathecal meperidine for surgical anesthesia.⁸⁶

The pattern of withdrawal symptoms after abrupt discontinuation of meperidine differs from that of morphine in that there are few autonomic nervous system effects. In addition, symptoms of withdrawal develop more rapidly and are of a shorter duration compared with those of morphine.

Fentanyl

Fentanyl is a phenylpiperidine-derivative synthetic opioid agonist that is structurally related to meperidine (see [Figure 7.1](#)). As an analgesic, fentanyl is 75 to 125 times more potent than morphine. It was first synthesized by Janssen Pharmaceutica in 1960 during an assay of meperidine derivatives and subsequently released as the citrate salt under the trade name Sublimaze.⁸⁷

Pharmacokinetics

A single dose of fentanyl administered IV has a more rapid onset and shorter duration of action than morphine. Despite the clinical impression that fentanyl produces a rapid onset, there is a distinct time lag between the peak plasma fentanyl concentration and peak slowing on the EEG. This delay reflects the effect-site equilibration time between blood and the brain for fentanyl, which is 6.4 minutes. The greater potency and more rapid onset of action reflect the greater lipid solubility of fentanyl compared with that of morphine, which facilitates its passage across the blood–brain barrier. Consequently, plasma concentrations of fentanyl (unlike morphine) correlate well with CSF concentrations. Likewise, the short duration of action of a single dose of fentanyl reflects its rapid redistribution to inactive tissue sites such as fat and skeletal muscles, with an associated decrease in the plasma concentration of the drug ([Figure 7.12](#)).⁸⁸

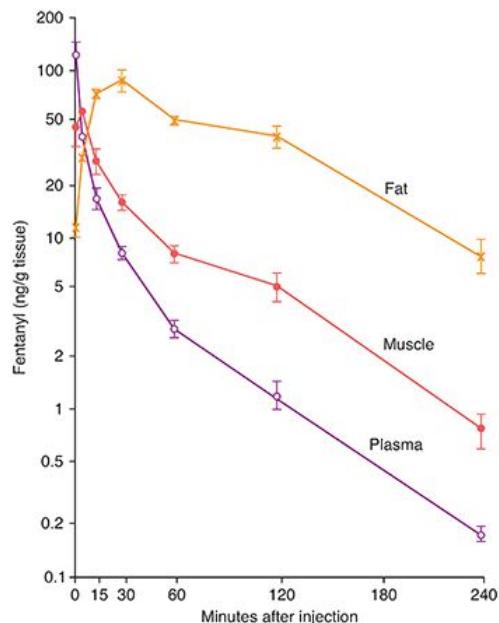


FIGURE 7.12 The short duration of action of a single intravenous dose of fentanyl reflects its rapid redistribution to inactive tissue sites such as fat and skeletal muscles, with associated decreases in the plasma concentration of drug (mean \pm standard error). *Reprinted with permission from Hug CC Jr, Murphy MR. Tissue redistribution of fentanyl and termination of its effects in rats. Anesthesiology. 1981;55(4):369-375. Copyright © 1981 American Society of Anesthesiologists, Inc.*

The lungs also serve as a large inactive storage site, with an estimated 75% of the initial fentanyl dose undergoing first-pass pulmonary uptake.⁶⁰ This nonrespiratory function of the lungs limits the initial amount of drug that reaches the systemic circulation and may play an important role in determining the pharmacokinetic profile of fentanyl. When multiple IV doses of fentanyl are administered or when there is

continuous infusion of the drug, progressive saturation of these inactive tissue sites occurs. As a result, the plasma concentration of fentanyl does not decrease rapidly, and the duration of analgesia, as well as depression of ventilation, may be prolonged. Cardiopulmonary bypass causes clinically insignificant effects on the pharmacokinetics of fentanyl despite associated hemodilution, hypothermia, nonphysiologic blood flow, and cardiopulmonary bypass–induced systemic inflammatory responses.⁸⁹

Metabolism

Fentanyl is extensively metabolized by N-demethylation, producing norfentanyl, hydroxyproprionyl-fentanyl, and hydroxyproprionyl-norfentanyl. Norfentanyl is structurally similar to normeperidine and is the principal metabolite of fentanyl in humans. It is excreted by the kidneys and can be detected in the urine for 72 hours after a single IV dose of fentanyl. Less than 10% of fentanyl is excreted unchanged in the urine. The pharmacologic activity of fentanyl metabolites is believed to be minimal.⁹⁰ Fentanyl is a substrate for hepatic P-450 enzymes (CYP3A) and is susceptible to drug interactions that reflect interference with enzyme activity (less likely than with alfentanil).⁹¹

Elimination Half-Time

Despite the clinical impression that fentanyl has a short duration of action, its elimination half-time is longer than that for morphine (see [Table 7.4](#)). This longer elimination half-time reflects a larger Vd of fentanyl because clearance of both opioids is similar (see [Table 7.4](#)). The larger Vd of fentanyl is due to its greater lipid solubility and thus more rapid passage into tissues compared with the less lipid-soluble morphine. After an IV bolus, fentanyl distributes rapidly from the plasma to highly vascular tissues (brain, lungs, heart). More than 80% of the injected dose leaves the plasma in <5 minutes. The plasma concentrations of fentanyl are maintained by slow reuptake from inactive tissue sites, which accounts for persistent drug effects that parallel the prolonged elimination half-time. In animals, the elimination half-time, Vd, and clearance of fentanyl are independent of the dose of opioid between 6.4 and 640 µg/kg IV.⁹²

A prolonged elimination half-time for fentanyl in elderly patients is due to decreased clearance of the opioid because Vd is not changed in comparison with younger adults.⁹³ This change may reflect age-related decreases in hepatic blood flow, microsomal enzyme activity, or albumin production, as fentanyl is highly bound (79%-87%) to protein. For these reasons, it is likely that a given dose of fentanyl will be effective for a longer period of time in elderly patients than in younger patients. A prolonged elimination half-time of fentanyl has also been observed in patients undergoing abdominal aortic surgery requiring infrarenal aortic cross-clamping.⁹⁴ Somewhat surprising, however, is the failure of hepatic cirrhosis to prolong significantly the elimination half-time of fentanyl.⁹⁵

Context-Sensitive Half-Time

As the duration of continuous infusion of fentanyl increases beyond about 2 hours, the context-sensitive half-time of this opioid becomes greater than sufentanil ([Figure 7.13](#)).^{3,96} This reflects saturation of inactive tissue sites with fentanyl during prolonged infusions and return of the opioid from peripheral compartments to the plasma. This tissue reservoir of fentanyl replaces fentanyl eliminated by hepatic metabolism so as to slow the rate of decrease in the plasma concentration of fentanyl when the infusion is discontinued.

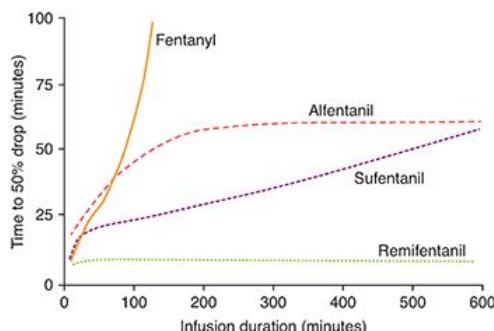


FIGURE 7.13 Computer simulation-derived context-sensitive half-times (time necessary for the plasma concentration to decrease 50% after discontinuation of the infusion) as a function of the duration of the intravenous infusion. Reprinted with permission from Egan TD, Lemmens HJM, Fiset P, et al. The pharmacokinetics of the new short-acting opioid remifentanil (GI87084B) in healthy adult male volunteers. *Anesthesiology*. 1993;79(5):881-892. Copyright © 1993 American Society of Anesthesiologists, Inc.

Cardiopulmonary Bypass

All opioids show a decrease in plasma concentration with initiation of cardiopulmonary bypass.⁹⁷ Simulations of multiple anesthetic drugs are provided online by Dr. Steven Shafer (<http://stompump.io>). The degree of this decrease is greater with fentanyl because a significant proportion of the drug adheres to the surface of the cardiopulmonary bypass circuit. The decrease is least with opioids that have a large Vd such that the addition of prime volume is less important. In this respect, sufentanil and alfentanil⁹⁸ may provide more stable plasma concentrations during cardiopulmonary bypass. Elimination of fentanyl and alfentanil has been shown to be prolonged by cardiopulmonary bypass.

Clinical Uses

Fentanyl is administered clinically in a wide range of doses. For example, low doses of fentanyl, 1 to 2 µg/kg IV, are injected to provide analgesia. Larger doses may be administered as an adjuvant to inhaled anesthetics in an attempt to blunt circulatory responses to (1) direct laryngoscopy for intubation of the trachea or (2) sudden changes in the level of surgical stimulation. Timing of the IV injection of fentanyl to prevent or treat such responses should consider the effect-site equilibration time, which for fentanyl is prolonged compared with alfentanil and remifentanil. Injection of an opioid such as fentanyl before painful surgical stimulation may decrease the subsequent amount of opioid required in the postoperative period to provide analgesia.⁵³ Administration of fentanyl 1.5 or 3 µg/kg IV 5 minutes before induction of anesthesia decreases the subsequent doses of isoflurane or desflurane with 60% nitrous oxide needed to block the sympathetic nervous system response to surgical stimulation (Figure 7.14).⁹⁹ Large doses of fentanyl, 50 to 150 µg/kg IV, have been used alone to produce surgical anesthesia. Large doses of fentanyl as the sole anesthetic have the advantage of stable hemodynamics due principally to the (1) lack of direct myocardial depressant effects, (2) absence of histamine release, and (3) suppression of the stress responses to surgery. Disadvantages of using fentanyl as the sole anesthetic include (1) failure to prevent sympathetic nervous system responses to painful surgical stimulation at any dose, especially in patients with good left ventricular function, (2) unpredictable amnestic effects potentially leading to recall, and (3) postoperative depression of ventilation.¹⁰⁰⁻¹⁰² Intrathecal fentanyl (maximal benefit achieved with 25 µg) can produce rapid, profound analgesia for early labor with minimal side effects.¹⁰³

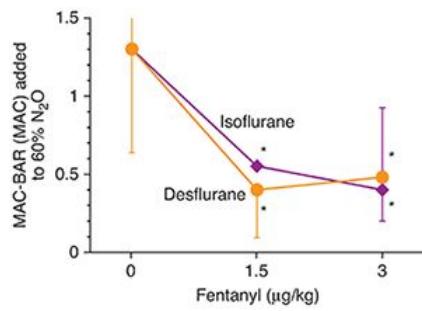


FIGURE 7.14 The anesthetic dose of desflurane and isoflurane required to block the adrenergic response (MAC-BAR) to incision in 50% of patients without and with fentanyl. There was no significant difference between the inhaled anesthetics at any fentanyl dose and both doses of fentanyl significantly and similarly decreased MAC-BAR (*P < .05; mean ± standard deviation). Reprinted with permission from Daniel M, Weiskopf RB, Noorani M, et al. Fentanyl augments the blockade of the sympathetic response to incision

(MAC-BAR) produced by desflurane and isoflurane. Desflurane and isoflurane MAC-BAR without and with fentanyl. Anesthesiology. 1998;88(1):43-49. Copyright © 1998 American Society of Anesthesiologists, Inc.

Fentanyl may be administered as a transmucosal preparation (oral transmucosal fentanyl) in a delivery device (lozenge mounted on a handle) designed to deliver 5 to 20 µg/kg of fentanyl. The goal is to decrease preoperative anxiety and facilitate the induction of anesthesia, especially in children.^{104,105} In children 2 to 8 years of age, the preoperative administration of oral transmucosal fentanyl, 15 to 20 µg/kg 45 minutes before the induction of anesthesia, reliably induces preoperative sedation and facilitates induction of inhalation anesthesia.¹⁰⁶ These same patients, however, are likely to experience decreases in breathing frequency and arterial oxygenation and an increased incidence of postoperative nausea and vomiting. In children 6 years of age and younger, the preoperative administration of oral transmucosal fentanyl, 15 µg/kg, is associated with an unacceptably high incidence of preoperative vomiting.¹⁰⁷ Conversely, another report did not observe an increased incidence of vomiting or arterial oxygen desaturation after premedication with oral transmucosal fentanyl.¹⁰⁸ For treatment of postoperative pain after orthopedic surgery, 1 mg of oral transmucosal fentanyl is equivalent to 5 mg of IV morphine.¹⁰⁹ Patients experiencing pain due to cancer may self-administer this opioid to the extent necessary to produce a desirable level of analgesia.

Transdermal fentanyl preparations delivering 75 to 100 µg/hour result in peak plasma fentanyl concentrations in about 18 hours that tend to remain stable during the presence of the patch, followed by a decreasing plasma concentration for several hours after removal of the delivery system. Transdermal fentanyl systems applied before the induction of anesthesia and left in place for 24 hours decrease the amount of parenteral opioid required for postoperative analgesia.¹¹⁰ Acute toxic delirium has been observed in patients with chronic pain due to cancer being treated with transdermal fentanyl for prolonged periods of time.¹¹¹ It is possible that renal failure and accumulation of norfentanyl contribute to the possible toxic effects of prolonged use of transdermal fentanyl. Evidence of opioid overdose has been observed when an upper body warming blanket was placed intraoperatively and came into contact with the fentanyl patch.¹¹²

Side Effects

The side effects of fentanyl resemble those described for morphine. Persistent or recurrent depression of ventilation due to fentanyl is a potential postoperative problem.¹¹³ Secondary peaks in plasma concentrations of fentanyl and morphine have been attributed to sequestration of fentanyl in acidic gastric fluid (ion trapping). Sequestered fentanyl could then be absorbed from the more alkaline small intestine back into the circulation to increase the plasma concentration of opioid and cause depression of ventilation to recur.¹¹⁴ This, however, may not be the mechanism for the secondary peak of fentanyl because reabsorbed opioid from the gastrointestinal tract or skeletal muscles, as evoked by movement associated with transfer from the operating room, would be subject to first-pass hepatic metabolism. An alternative explanation for the secondary peak of fentanyl is washout of opioid from the lungs as ventilation to perfusion relationships are reestablished in the postoperative period.

Cardiovascular Effects

Unlike morphine, fentanyl, even in large doses (50 µg/kg IV), does not evoke the release of histamine (see [Figure 7.4](#)).²⁶ As a result, dilatation of venous capacitance vessels leading to hypotension is unlikely. Carotid sinus baroreceptor reflex control of heart rate is markedly depressed by fentanyl, 10 µg/kg IV, administered to neonates ([Figure 7.15](#)).¹¹⁵ Therefore, changes in systemic blood pressure occurring during fentanyl anesthesia have to be carefully considered because cardiac output is principally rate dependent in neonates. Bradycardia is more prominent with fentanyl than morphine and may lead to occasional decreases in blood pressure and cardiac output.

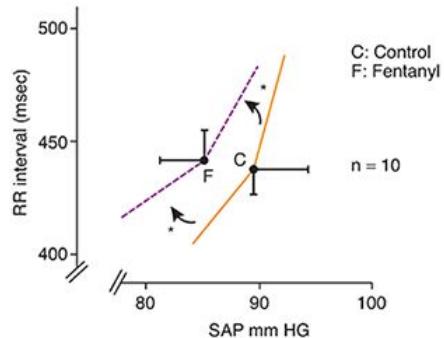


FIGURE 7.15 Fentanyl depresses the carotid sinus reflex-mediated heart rate response to changes in blood pressure in neonates ($*P < .02$). Abbreviation: SAP, systemic arterial pressure. Reprinted with permission from Murat I, Levron JC, Berg A, et al. Effects of fentanyl on baroreceptor reflex control of heart rate in newborn infants. *Anesthesiology*. 1988;68(5):717-722. Copyright © 1988 American Society of Anesthesiologists, Inc.

Seizure Activity

Seizure-like activity has been described to follow rapid IV administration of fentanyl, sufentanil, and alfentanil.¹¹⁶ In the absence of EEG evidence of seizure activity, however, it is difficult to distinguish opioid-induced skeletal muscle rigidity or myoclonus from seizure activity. Indeed, recording of the EEG during periods of opioid-induced skeletal muscle rigidity fails to reveal evidence of seizure activity in the brain.¹¹⁷ Even plasma concentrations as high as 1,750 ng/mL after rapid administration of fentanyl, 150 µg/kg IV, do not produce EEG evidence of seizure activity.¹¹⁸ Conversely, opioids might produce a form of myoclonus secondary to depression of inhibitory neurons that would produce a clinical picture of seizure activity in the absence of EEG changes.

Somatosensory-Evoked Potentials and Electroencephalogram

Fentanyl in doses exceeding 30 µg/kg IV produces changes in somatosensory-evoked potentials that, although detectable, do not interfere with the use and interpretation of this monitor during anesthesia.¹¹⁹ Opioids, including fentanyl, attenuate skeletal muscle movement at doses that have little effect on the EEG. This suggests that movement in response to surgical skin incision (used to measure minimum alveolar concentration [MAC]) primarily reflects the ability of a drug to obtund noxious reflexes and may not be the most appropriate measure for assessing consciousness or loss of consciousness.¹²⁰

Intracranial Pressure

Administration of fentanyl and sufentanil to head injury patients has been associated with modest increases (6-9 mm Hg) in ICP despite maintenance of an unchanged PaCO_2 .¹²¹ These increases in ICP are typically accompanied by decreases in mean arterial pressure and cerebral perfusion pressure. In fact, increases in ICP do not accompany the administration of sufentanil when changes in mean arterial pressure are prevented (Figure 7.16).¹²² This suggests that increases in ICP evoked by sufentanil (and presumably fentanyl) may have been due to autoregulatory decreases in cerebral vascular resistance due to decreases in systemic blood pressure resulting in vasodilation, increased blood volume, and increased ICP. Nevertheless, opioid-induced increases in ICP are similar in the presence of intact or impaired autoregulation suggesting that mechanisms other than activation of the vasodilatory cascade need to be considered.¹²³

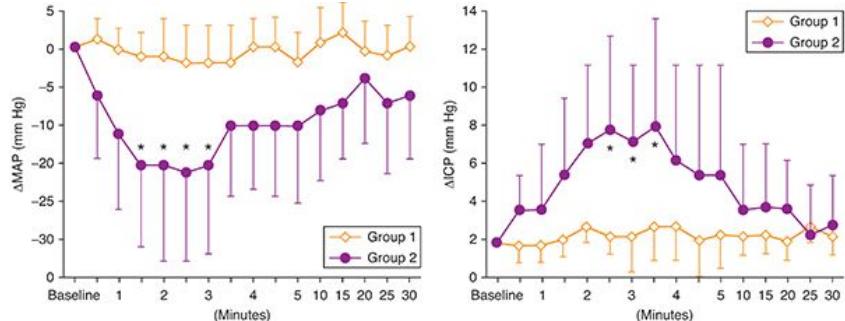


FIGURE 7.16 Changes in mean arterial pressure (MAP) and intracranial pressure (ICP) before and after administration of sufentanil, 3 $\mu\text{g}/\text{kg}$ intravenously, to 30 patients with intracranial hypertension after severe brain trauma. The ICP increased only in those patients who experienced a decrease in MAP after administration of sufentanil (mean \pm standard deviation; * $P < .05$ vs group I). *Reprinted with permission from Werner C, Kochs E, Bause H, et al. Effects of sufentanil on cerebral hemodynamics and intracranial pressure in patients with brain injury. Anesthesiology. 1995;83(4):721-726. Copyright © 1995 American Society of Anesthesiologists, Inc.*

Drug Interactions

Analgesic concentrations of fentanyl greatly potentiate the effects of benzodiazepines and decrease the dose requirements of propofol. The opioid-benzodiazepine combination displays marked synergism with respect to hypnosis and depression of ventilation.¹²⁴ In clinical practice, the advantage of synergy between opioids and benzodiazepines for the maintenance of patient comfort is carefully weighed against the disadvantages of the potentially adverse depressant effects of this combination.

Sufentanil

First synthesized in 1974, sufentanil is a thienyl analogue of fentanyl (see [Figure 7.1](#)). The analgesic potency of sufentanil is 5 to 10 times that of fentanyl, which parallels the greater affinity of sufentanil for opioid receptors compared with that of fentanyl. Based on the plasma concentration necessary to cause 50% of the maximum slowing on the EEG (EC50), sufentanil is 12 times more potent than fentanyl.¹²⁵ Transient skeletal muscle spasm has been described after the accidental intrathecal injection of a large dose of sufentanil (40 μg), suggesting an irritant effect of the opioid.¹²⁶

Pharmacokinetics

The elimination half-time of sufentanil is intermediate between that of fentanyl and alfentanil (see [Table 7.4](#)).¹²⁷ A single IV dose of sufentanil has a similar elimination half-time in patients with or without cirrhosis of the liver.¹²⁸ A prolonged elimination half-time has been observed in elderly patients receiving sufentanil for abdominal aortic surgery.¹²⁹ The Vd and elimination half-time of sufentanil is increased in obese patients, which most likely reflects the high lipid solubility of this opioid.¹³⁰

A high tissue affinity is consistent with the lipophilic nature of sufentanil, which permits rapid penetration of the blood-brain barrier and onset of CNS effects (effect-site equilibration time of 6.2 minutes is similar to that of 6.8 minutes for fentanyl).¹²⁵ A rapid redistribution to inactive tissue sites terminates the effect of small doses, but a cumulative drug effect can accompany large or repeated doses of sufentanil.

Sufentanil undergoes significant first-pass pulmonary uptake (approximately 60%) after rapid IV injection.¹³¹ This pulmonary first-pass uptake is similar to fentanyl and greater than morphine (about 7%) and alfentanil (about 10%).

The extensive protein binding of sufentanil (92.5%) compared with that of fentanyl (79%-87%) contributes to a smaller Vd, which is characteristic of sufentanil. Binding to α_1 -acid glycoprotein constitutes a principal proportion of the total plasma protein binding of sufentanil. Levels of α_1 -acid glycoprotein vary over a threefold range in healthy volunteers and are increased after surgery, which could result in a decrease

in the plasma concentration of pharmacologically active unbound sufentanil. Lower concentrations of α_1 -acid glycoprotein in neonates and infants probably account for decreases in protein binding of sufentanil in these age groups compared with that in older children and adults.¹³² The resulting increased free fraction of sufentanil in the neonate might contribute to enhanced effects of this opioid. Indeed, fentanyl and its derivatives produce anesthesia and depression of ventilation at lower doses in neonates than in adults.¹³³

Metabolism

Sufentanil is rapidly metabolized by *N*-dealkylation at the piperidine nitrogen and by *O*-demethylation. The products of *N*-dealkylation are pharmacologically inactive, whereas desmethyl sufentanil has about 10% of the activity of sufentanil. Less than 1% of an administered dose of sufentanil appears unchanged in urine. Indeed, the high lipid solubility of sufentanil results in maximal renal tubular reabsorption of free drug as well as its enhanced access to hepatic microsomal enzymes. Extensive hepatic extraction means that clearance of sufentanil will be sensitive to changes in hepatic blood flow but not to alterations in the drug-metabolizing capacity of the liver. Sufentanil metabolites are excreted almost equally in urine and feces, with about 30% appearing as conjugates. The production of a weakly active metabolite and the substantial amount of conjugated metabolite formation imply the possible importance of normal renal function for the clearance of sufentanil. Indeed, prolonged depression of ventilation in association with an abnormally increased plasma concentration of sufentanil has been observed in a patient with chronic renal failure.¹³⁴

Context-Sensitive Half-Time

The context-sensitive half-time of sufentanil is actually less than that for alfentanil for continuous infusions of up to 8 hours in duration (see [Figure 7.13](#)).³ This shorter context-sensitive half-time can be explained in part by the large *Vd* of sufentanil compared to alfentanil. After termination of a sufentanil infusion, the decrease in the plasma drug concentration is accelerated not only by metabolism but also by continued redistribution of sufentanil into peripheral tissue compartments. Compared with alfentanil, sufentanil may have a more favorable recovery profile when used over a longer period of time. Conversely, alfentanil has a pharmacokinetic advantage for the treatment of discrete and transient noxious stimuli because its short effect-site equilibration time allows rapid access of the drug to the brain and facilitates titration.

Clinical Uses

In volunteers, a single dose of sufentanil, 0.1 to 0.4 $\mu\text{g}/\text{kg}$ IV, produces a longer period of analgesia and less depression of ventilation than does a comparable dose of fentanyl (1-4 $\mu\text{g}/\text{kg}$ IV).¹³⁵ Compared with large doses of morphine or fentanyl, sufentanil, 18.9 $\mu\text{g}/\text{kg}$ IV, results in more rapid induction of anesthesia, earlier emergence from anesthesia, and earlier tracheal extubation.¹³⁶ As observed with other opioids, sufentanil causes a decrease in cerebral metabolic oxygen requirements and cerebral blood flow is also decreased or unchanged.¹³⁷ Bradycardia produced by sufentanil may be sufficient to decrease cardiac output. As observed with fentanyl, delayed depression of ventilation has also been described after the administration of sufentanil.¹³⁸

Although large doses of sufentanil (10-30 $\mu\text{g}/\text{kg}$ IV) or fentanyl (50-150 $\mu\text{g}/\text{kg}$ IV) produce minimal hemodynamic effects in patients with good left ventricular function, the systemic blood pressure and hormonal (catecholamine) responses to painful stimulation such as median sternotomy are not predictably prevented.¹³⁹ It seems unlikely that any clinically useful dose of sufentanil or fentanyl will abolish such responses in all patients. Use of large doses of opioids, including sufentanil or fentanyl, to produce IV induction of anesthesia may result in rigidity of chest and abdominal musculature. This skeletal muscle rigidity makes ventilation of the patient's lungs with positive airway pressure difficult. As with fentanyl, difficult ventilation during sufentanil-induced skeletal muscle rigidity may actually reflect obstruction at the level of the glottis or above, which can be overcome by tracheal intubation.¹⁴⁰

Alfentanil

Alfentanil is an analogue of fentanyl that is less potent (one-fifth to one-tenth) and has one-third the duration of action of fentanyl (see [Figure 7.2](#)). It was first synthesized in 1976. A unique advantage of alfentanil compared with fentanyl and sufentanil is the more rapid onset of action (rapid effect-site equilibration) after the IV administration of alfentanil. For example, the effect-site equilibration time for alfentanil is 1.4 minutes compared with 6.8 and 6.2 minutes for fentanyl and sufentanil, respectively (see [Table 7.4](#)).^{4,141}

Pharmacokinetics

Alfentanil has a short elimination half-time compared with fentanyl and sufentanil (see [Table 7.4](#)). Cirrhosis of the liver, but not cholestatic disease, prolongs the elimination half-time of alfentanil.¹⁴² Renal failure does not alter the clearance or elimination half-time of alfentanil.¹⁴³ The elimination half-time of alfentanil is shorter in children (4–8 years old) than adults, reflecting a smaller Vd in these younger patients.¹⁴⁴

The rapid effect-site equilibration characteristic of alfentanil is a result of the low pK_a of this opioid such that nearly 90% of the drug exists in the nonionized form at physiologic pH. It is the nonionized fraction that readily crosses the blood–brain barrier. The rapid peak effect of alfentanil at the brain is useful when an opioid is required to blunt the response to a single, brief stimulus such as tracheal intubation or performance of a retrobulbar block.

The Vd of alfentanil is 4 to 6 times smaller than that of fentanyl (see [Table 7.4](#)).¹⁴⁵ This smaller Vd compared with that of fentanyl reflects lower lipid solubility and higher protein binding. Despite this lesser lipid solubility, penetration of the blood–brain barrier by alfentanil is rapid because of its large nonionized fraction at physiologic pH. Alfentanil is principally bound to α_1 -acid glycoprotein, a protein whose plasma concentration is not altered by liver disease. Because protein binding is similar, it is likely that a decreased percentage of adipose tissue in children is responsible for the short elimination half-time.

Metabolism

Alfentanil is metabolized predominantly by two independent pathways: piperidine N-dealkylation to noralfentanil and amide N-dealkylation to N-phenylpropionamide. Noralfentanil is the major metabolite recovered in urine, with <0.5% of an administered dose of alfentanil being excreted unchanged. The efficiency of hepatic metabolism is emphasized by clearance of about 96% of alfentanil from the plasma within 60 minutes of its administration.

Attempts to develop reliable infusion regimens to attain and maintain specific plasma concentrations of alfentanil have been confounded by the wide interindividual variability in alfentanil pharmacokinetics. The most significant factor responsible for unpredictable alfentanil disposition is the 10-fold interindividual variability in alfentanil systemic clearance, presumably reflecting variability in hepatic intrinsic clearance. In this regard, it is likely that population variability in P-450 3A4 (CYP3A4) activity (most abundant P-450 hepatic enzyme and the major isoform of P-450 responsible for alfentanil metabolism and clearance) is the mechanistic explanation for the interindividual variability in alfentanil disposition.¹⁴⁶ Alfentanil clearance is markedly influenced by CYP3A activity, and alfentanil is a sensitive and validated probe for CYP3A activity.⁹¹ Alterations in P-450 activity may be responsible for the ability of erythromycin to inhibit the metabolism of alfentanil and a resulting prolonged opioid effect.¹⁴⁷

Context-Sensitive Half-Time

The context-sensitive half-time of alfentanil is actually longer than that of sufentanil for infusions up to 8 hours in duration (see [Figure 7.13](#)).⁹⁶ This phenomenon can be explained in part by the large Vd of sufentanil. After termination of a continuous infusion of sufentanil, the decrease in the plasma drug concentration is accelerated not only by metabolism but also by continued redistribution of sufentanil into peripheral compartments. Conversely, the Vd of alfentanil equilibrates rapidly; therefore, peripheral distribution of drug away from the plasma is not a significant contributor to the decrease in the plasma concentration after discontinuation of the alfentanil infusion. Thus, despite the short elimination half-time of alfentanil, it may not necessarily be a superior choice to sufentanil for ambulatory sedation techniques.

Clinical Uses

Alfentanil has a rapid onset and offset of intense analgesia reflecting its very prompt effect-site equilibration. This characteristic of alfentanil is used to provide analgesia when the noxious stimulation is acute but transient as associated with laryngoscopy and tracheal intubation and performance of a retrobulbar block. For example, administration of alfentanil, 15 µg/kg IV, about 90 seconds before beginning direct laryngoscopy is effective in blunting the systemic blood pressure and heart rate response to tracheal intubation.¹⁴⁸ The catecholamine response to this noxious stimulation is also blunted by alfentanil, 30 µg/kg IV.¹⁴⁸ Alfentanil in doses of 10 to 20 µg/kg IV blunts the circulatory but not the catecholamine release response to the sudden exposure to high inhaled concentrations of desflurane.¹⁴⁹ Alfentanil, 150 to 300 µg/kg IV, administered rapidly, produces unconsciousness in about 45 seconds. After this induction, maintenance of anesthesia can be provided with a continuous infusion of alfentanil, 25 to 150 µg/kg/hour IV, combined with an inhaled anesthetic.¹⁵⁰ Unlike other opioids, supplemental doses of alfentanil seem to be more likely to decrease systemic blood pressure that is increased after painful stimulation. Alfentanil increases biliary tract pressures similarly to fentanyl.

Remifentanil

Remifentanil is a selective µ-opioid agonist with an analgesic potency similar to that of fentanyl (15–20 times as potent as alfentanil) and a blood–brain equilibration (effect-site equilibration) time similar to that of alfentanil (see [Table 7.4](#)).^{23,151–153} Although chemically related to the fentanyl family of short-acting phenylpiperidine derivatives, remifentanil is structurally unique because of its ester linkage (see [Figure 7.1](#)). Remifentanil's ester structure renders it susceptible to hydrolysis by nonspecific plasma and tissue esterases to inactive metabolites.³ This unique pathway of metabolism leads to (1) brief action, (2) precise and rapidly titratable effect due to its rapid onset and offset, (3) lack of accumulation, and (4) rapid recovery after discontinuation of its administration.

Ventilation

After administration of 0.5 µg/kg IV remifentanil, there is a decrease in the slope and downward shift of the carbon dioxide ventilatory response curve that reaches its nadir after about 150 seconds following injection ([Figure 7.17](#)).¹⁵⁴ Recovery after this small dose of remifentanil was complete within about 15 minutes. The combination of remifentanil and propofol is synergistic resulting in severe depression of ventilation ([Figure 7.18](#)).¹⁵⁵

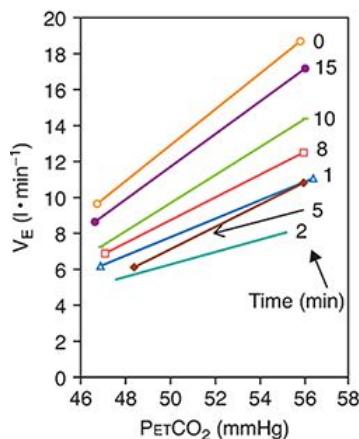


FIGURE 7.17 Carbon dioxide response curves before (time = 0) and at selected times after administration of 0.5 µg/kg intravenously remifentanil. Abbreviations: PETCO₂, end-tidal PCO₂; VE, minute ventilation.

Reprinted with permission from Babenco HD, Conard PF, Gross JB. The pharmacodynamic effect of a remifentanil bolus on ventilatory control. Anesthesiology. 2000;92(2):393-398. Copyright © 2000 American Society of Anesthesiologists, Inc.

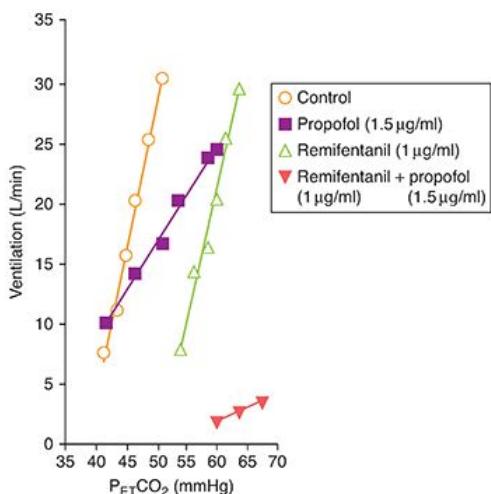


FIGURE 7.18 Ventilatory response curves from one individual. The combined administration of remifentanil and propofol decreased the slope of the carbon dioxide response curve and caused a rightward shift. Abbreviation: $P_{ET}CO_2$, end-tidal PCO_2 . Reprinted with permission from Nieuwenhuijs DJ, Olofsen E, Romberg RR, et al. Response surface modeling of remifentanil-propofol interaction on cardiorespiratory control and bispectral index. Anesthesiology. 2003;98(2):312-322. Copyright © 2003 American Society of Anesthesiologists, Inc.

Pharmacokinetics

The pharmacokinetics of remifentanil is characterized by small V_d , rapid clearance, and low interindividual variability compared to other IV anesthetic drugs. The rapid metabolism of remifentanil and its small V_d mean that remifentanil will accumulate less than other opioids. Because of its rapid systemic clearance, remifentanil provides pharmacokinetic advantages in clinical situations requiring predictable termination of drug effect. Remifentanil's pharmacokinetics is similar in obese and lean patients. Therefore, dosing regimens should be based on ideal (lean) body mass rather than total body weight.¹⁵⁶

The most salient pharmacokinetic feature of remifentanil is the extraordinary clearance of nearly 3 L/min, which is about 8 times more rapid than that of alfentanil. Remifentanil has a smaller V_d than alfentanil. The combination of rapid clearance and small V_d produces a drug with a uniquely transient effect. In fact, the rate of decline (context-sensitive half-time) of the remifentanil plasma concentration will be nearly independent of the infusion duration (see [Figure 7.13](#)).^{2,3} The rapid effect-site equilibration means that a remifentanil infusion rate will promptly approach steady state in the plasma and its effect site. It is estimated that remifentanil plasma concentrations will reach a steady state within 10 minutes of beginning an infusion. The relationship between infusion rate and opioid concentration will be less variable for remifentanil than for other opioids. Furthermore, the rapid clearance of remifentanil, combined with the rapid blood–brain equilibration, means changes in infusion rates will be paralleled by prompt changes in drug effect.

Based on analysis of the EEG response, it is estimated that remifentanil is about 19 times more potent than alfentanil (EC50 for EEG depression 20 ng/mL vs 376 ng/mL).³ The effect-site equilibration time, however, is similar for both opioids, suggesting that remifentanil will have an alfentanil-like onset (see [Table 7.4](#)). For example, after a rapid IV injection, the peak effect-site concentration of remifentanil will be present within 1.1 minutes, compared with 1.4 minutes for alfentanil. The effect, however, will be more transient after administration of remifentanil than alfentanil.

Metabolism

Remifentanil is unique among the opioids in undergoing metabolism by nonspecific plasma and tissue esterases to inactive metabolites.³ The principal metabolite, remifentanil acid, is 300- to 4,600-fold less potent than remifentanil as a μ agonist and is excreted primarily by the kidneys. *N*-dealkylation of remifentanil is a minor metabolic pathway in humans. Remifentanil does not appear to be a substrate for butyrylcholinesterases (pseudocholinesterase), and thus, its clearance should not be affected by cholinesterase deficiency or anticholinergics.² Additionally, it is likely that remifentanil's pharmacokinetics will be unchanged by renal or hepatic failure because esterase metabolism is usually preserved in these states.¹⁵⁷ In this regard, the clearance of remifentanil is not altered during the anhepatic phase of liver transplantation. Hypothermic cardiopulmonary bypass decreases clearance of remifentanil by an average of 20%, presumably reflecting the effect of temperature on blood and tissue esterase activity. Esterase metabolism appears to be a very well-preserved metabolic system with little variability between individuals, which contributes to the predictability of drug effect associated with the infusion of remifentanil.

Context-Sensitive Half-Time

Context-sensitive half-time for remifentanil is independent of the duration of infusion and is estimated to be about 4 minutes.^{2,158} This drug's rapid clearance is responsible for the lack of accumulation even during prolonged periods of infusion. In contrast, the context-sensitive half-times for sufentanil, alfentanil, and fentanyl are longer and depend significantly on the duration of the infusion (see [Table 7.4](#)).

Clinical Uses

The clinical uses of remifentanil reflect the unique pharmacokinetics of this drug, which allow rapid onset of drug effect, precise titration to the desired effect, the ability to maintain a sufficient effect site concentration to suppress the stress response, and rapid recovery from the drug's effects. In cases where a profound analgesic effect is desired transiently (performance of a retrobulbar block), remifentanil may be useful. Prompt onset and short duration of action make remifentanil a useful selection for suppression of the transient sympathetic nervous system response to direct laryngoscopy and tracheal intubation in at-risk patients.¹⁵⁹ Intermittent remifentanil administered as PCA is an alternative (albeit not optimal) analgesic strategy during labor and delivery for those unwilling or unable to receive neuraxial analgesia.¹⁶⁰ One additional benefit during labor would be rapid clearance from the neonatal circulation as well, thus reducing the risk of neonatal depression.¹⁶¹ Conceivably, remifentanil could be used for long operations, when a quick recovery time is desired (neurologic assessment, wake-up test) but at a significantly higher cost than other opioids.

Anesthesia can be induced with remifentanil, 1 μ g/kg IV administered over 60 to 90 seconds, or with a gradual initiation of the infusion at 0.5 to 1.0 μ g/kg IV for about 10 minutes, before administration of a standard hypnotic prior to tracheal intubation.¹⁶² The dose of hypnotic drug may need to be decreased to compensate for the synergistic effect with remifentanil. Remifentanil can be used as the analgesic component of a general anesthetic (0.25-1.00 μ g/kg IV or 0.05-2.00 μ g/kg/minute IV) or sedation techniques with the ability to rapidly recover from undesirable effects such as opioid-induced depression of ventilation or excessive sedation. Remifentanil, 0.05 to 0.10 μ g/kg/minute in combination with midazolam, 2 mg IV, provides effective sedation and analgesia during monitored anesthesia care in otherwise healthy adult patients.¹⁶³ Midazolam also produces a dose-dependent potentiation of remifentanil's depressant effect on breathing rate. Changes in remifentanil drug effect predictably follow changes in the infusion rate, making it possible to more precisely titrate to the desired response than with other opioids. Before cessation of the remifentanil infusion, a longer acting opioid should be administered to ensure analgesia when the patient awakens. The spinal or epidural administration of remifentanil is not recommended, as the safety of the vehicle (glycine, which acts as an inhibitory neurotransmitter) or opioid has not been determined.² Remifentanil, 100 μ g IV, attenuates the acute hemodynamic responses to electroconvulsive therapy and does not alter the duration of electroconvulsive-induced seizure activity.¹⁶⁴

Side Effects

The advantage of remifentanil possessing a short recovery period may be considered a disadvantage if the infusion is stopped suddenly, whether it be deliberate or accidental. It is important to administer a longer acting opioid for postoperative analgesia when remifentanil has been administered for this purpose intraoperatively. All fentanyl analogs, including remifentanil, have been reported to induce “seizure-like” activity.¹⁶⁵

Nausea and vomiting, depression of ventilation, and mild decreases in systemic blood pressure and heart rate may accompany the administration of remifentanil. Depression of ventilation produced by remifentanil is not altered by renal or liver dysfunction. Histamine release does not accompany the administration of remifentanil. ICP and intraocular pressure are not changed by remifentanil.^{166,167} High-dose remifentanil decreases cerebral blood flow and cerebral metabolic oxygen requirements without impairing cerebrovascular carbon dioxide reactivity.¹⁶⁸ Remifentanil delays drainage of dye from the gallbladder into the duodenum, but the delay is shorter than with other opioids.¹⁶⁹

Hyperalgesia

Initial reports suggested that intraoperative remifentanil infusion produces acute opioid tolerance and hyperalgesia (**Figure 7.19**).¹⁷⁰ In this regard, NMDA receptor antagonists such as ketamine and magnesium may be helpful. Subanesthetic ketamine has been shown to decrease morphine requirements and the development of hyperalgesia after intraoperative remifentanil use (**Figure 7.20**).^{50,171} Subsequent work, however, has questioned whether remifentanil-induced hyperalgesia is a true phenomenon.¹⁷² Regardless, it is important to know that patients on chronic pain medication preoperatively would require higher doses of opioids postoperatively compared to naive patients and small doses of ketamine would be an alternative therapeutic approach.

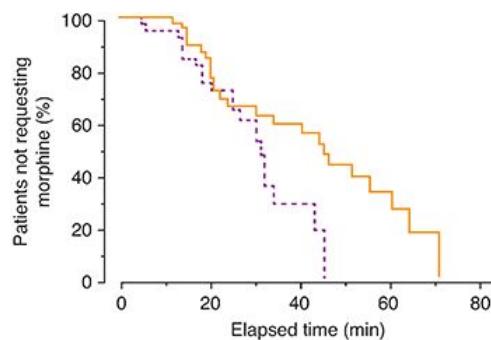


FIGURE 7.19 Cumulative curves for patients who did not request an additional morphine injection following discontinuation of remifentanil (dashed line) or desflurane (solid line). Reprinted with permission from Guignard B, Bossard AE, Coste C, et al. Acute opioid tolerance: Intraoperative Remifentanil increases postoperative pain and morphine requirement. Anesthesiology. 2000;93(2):409-417. Copyright © 2000 American Society of Anesthesiologists, Inc.

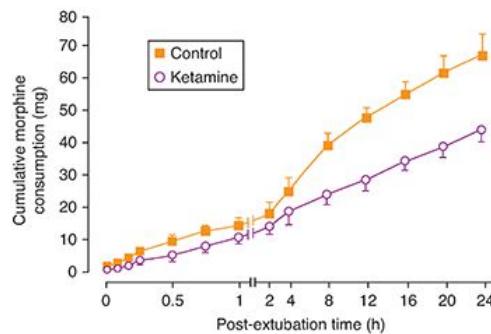


FIGURE 7.20 Cumulative postoperative morphine consumption in patients undergoing surgery with remifentanil infusions. Patients receiving subanesthetic ketamine infusions experienced less postoperative pain and required less morphine. *Reprinted with permission from Guignard B, Coste C, Costes H, et al. Supplementing desflurane-remifentanil anesthesia with small-dose ketamine reduces perioperative opioid analgesic requirements. Anesth Analg. 2002;95(1):103-108. Copyright © 2002 International Anesthesia Research Society.*

Opioid-induced hyperalgesia may develop with chronic (or even acute) use.¹⁷³ Although this is a complex topic, interaction of opioids with nonneuronal cells (such as microglia and mast cells) appears to play a central role in this phenomenon.¹⁷⁴

Opioids With Oral Bioavailability

All orally bioavailable opioids have been linked to persistent use and abuse. In the perioperative setting, preoperative oral opioid use is a strong predictor for continued postoperative use. This has been demonstrated for a large variety of surgical procedures.^{175,176}

Codeine

Codeine is the result of the substitution of a methyl group for the hydroxyl group on the number 3 carbon of morphine (see [Figure 7.1](#)). The presence of this methyl group limits first-pass hepatic metabolism and accounts for the efficacy of codeine when administered orally. The elimination half-time of codeine after oral or IM administration is 3.0 to 3.5 hours. About 10% of administered codeine is demethylated by CYP2D6 in the liver to morphine, which may be responsible for the analgesic effect of codeine, although codeine-6-glucuronide may also exert an analgesic effect.¹⁷⁷ Any remaining codeine is demethylated to inactive norcodeine, which is conjugated or excreted unchanged by the kidneys. The large variability in CYP2D6 activity (over 100 identified alleles) leads to variable analgesic effect from codeine-containing drugs; some patients who claim that codeine is an ineffective drug for them may in fact poorly metabolize it to active forms while rapid metabolizers will have an exaggerated effect.¹⁷⁸

Codeine is effective at suppressing cough at oral doses of 15 mg. Maximal analgesia, equivalent to that produced by 650 mg of aspirin, occurs with 60 mg of codeine. When administered IM, 120 mg of codeine is equivalent in analgesic effect to 10 mg of morphine. Most often, codeine is included in medications as an antitussive or is combined with nonopioid analgesics for the treatment of mild to moderate pain. The risk of physical dependence on codeine appears to be less than that of morphine and occurs only rarely after oral analgesic use. Codeine produces minimal sedation, nausea, vomiting, and constipation. Dizziness may occur in ambulatory patients. Even in large doses, codeine is unlikely to produce apnea. Administration of codeine IV is not recommended, because histamine-induced hypotension is likely. Due to reports of overdose and death (perhaps due to genetic variants increasing metabolism to active forms), codeine is also specifically contraindicated for children undergoing tonsillectomy or adenoidectomy and for breastfeeding mothers. The drug carries a US Food and Drug Administration “Black Box” warning for these populations.¹⁷⁹

Hydromorphone

First introduced in 1926, hydromorphone is a derivative of morphine that is about 5 times as potent as morphine but has a slightly shorter duration of action. It is less hydrophilic than morphine, leading to faster onset of analgesia. Hydromorphone is an effective alternative to morphine in the treatment of opioid-responsive moderate to severe pain.¹⁸⁰ The uses and side effects of hydromorphone are the same as those of morphine, although histamine release is less prominent with hydromorphone. Similar to other opioids, large doses of hydromorphone have been reported to cause agitation and myoclonus.¹⁸¹

Oxymorphone

Oxymorphone is the result of the addition of a hydroxyl group to hydromorphone. It is about 10 times as potent as morphine and seems to cause more nausea and vomiting. An oral preparation of oxymorphone

(immediate release) produces maximum plasma concentrations in 30 minutes with associated rapid onset of analgesia.¹⁸²

Oxycodone

Sustained-release oral oxycodone preparations provide stable plasma concentrations for the treatment of moderate to severe pain. Abuse potential is great including tampering (crushing and powdering) for IV or intranasal injection to obtain a rapid and powerful opioid effect.

Hydrocodone

A derivative of codeine, hydrocodone is a useful oral opioid, commonly combined with acetaminophen. The approval by the US Food and Drug Administration of one extended-release formulation (Zohydro) provoked much opposition due to its abuse potential and lack of abuse-deterrent features.¹⁸³ Originally classified as a schedule III drug (moderate abuse potential) in the United States, hydrocodone has subsequently been reclassified as schedule II (high abuse potential) due to increased reports of diversion and abuse.

Methadone

Methadone is a synthetic opioid agonist that produces analgesia in the setting of chronic pain syndromes and is highly effective by the oral route. The efficient oral absorption, prompt onset of action, and prolonged duration of action of methadone render this an attractive drug for one-daily dosing to suppress withdrawal symptoms and relapse in physically dependent persons. The IV formulation of methadone is useful intraoperatively but should not be used for postoperative analgesia in opioid-naïve patients due to increasing concentrations with multiple doses.

Opioid Withdrawal

Methadone can substitute for morphine at about one-fourth the dosage. Some of its analgesic benefit is due to NMDA antagonism. Controlled withdrawal from opioids using methadone is milder and less acute than that from morphine. This drug is metabolized in the liver to inactive substances that are excreted in the urine and bile with small amounts of unchanged drug.

The side effects of methadone (depression of ventilation, miosis, constipation, biliary tract spasm) resemble those of morphine. Its sedative and euphoric actions are less than those produced by morphine. Methadone-induced miosis is less prominent than that caused by morphine, and complete tolerance to this action can develop.

Treatment of Chronic Pain

NMDA receptor antagonist activity may also be useful in treatment of neuropathic pain and minimize the potential for development of tolerance. The principal disadvantage for use of methadone to treat chronic pain is its prolonged and unpredictable half-time. When methadone is administered more than once daily to opioid-naïve patients, as is common in treatment of chronic pain syndromes, the drug may accumulate and result in high plasma concentrations and associated depression of ventilation.¹⁸⁴ For this reason, slow-release formulations (such as oxycodone) may be preferable to methadone for the treatment of outpatient acute postoperative pain.

Tramadol

Tramadol is a centrally acting analgesic that has moderate affinity for μ receptors and weak α - and δ -opioid receptor affinity but is 5 to 10 times less potent than morphine as an analgesic.¹⁸⁵ In addition to μ -opioid agonist effects, tramadol enhances the function of the spinal descending inhibitory pathways by inhibition of neuronal reuptake of norepinephrine and 5-hydroxytryptamine (serotonin) as well as presynaptic stimulation of 5-hydroxytryptamine release. In volunteers, naloxone antagonized only an estimated 30% of the effect of tramadol.¹⁸⁶

Tramadol is a prodrug that is metabolized by CYP2D6 to the active compound O-desmethyltramadol. Thus, the same concerns about variability in effectiveness and adverse effects seen with codeine also apply to

tramadol. It is a racemic mixture of two enantiomers, one of which is responsible for inhibition of norepinephrine uptake, whereas the other is responsible for inhibition of 5-hydroxytryptamine reuptake and facilitation of its release, plus the actions of this drug at μ receptors. In this regard, tramadol may be an exception to the argument that chiral mixtures should be avoided when technology exists to prepare a single, pure isomer.¹⁸⁷

A marked decrease in postoperative shivering has been noted in treated patients, and the minimal depressant effects on breathing are useful.¹⁸⁸ Tramadol slows gastric emptying, although the effect is small compared with other opioids.¹⁸⁹ Toxicity from overdose can manifest as hypotension, bradycardia, seizures, coma, and rhabdomyolysis. Disadvantages of tramadol include its interaction with warfarin (Coumadin) anticoagulants (not all reports confirm this interaction) and the occurrence of serotonin syndrome and drug-related seizures (avoid in patients with epilepsy or those being treated with drugs that lower the seizure threshold such as antidepressants).^{190,191} A further drawback to the perioperative use of this drug as an analgesic is a high incidence of associated nausea and vomiting.

Heroin

Heroin (diacetylmorphine) is a synthetic opioid produced by acetylation of morphine. It was developed in 1898 and was originally claimed to have no addictive potential. When administered parenterally, heroin acts in a markedly different way than morphine. For example, there is rapid penetration of heroin into the brain, where it is hydrolyzed to the active metabolites monoacetylmorphine and morphine. The unique rapid entrance into the CNS is most likely caused by the lipid solubility and chemical structure of heroin. Compared with morphine, parenteral heroin has a (1) more rapid onset, (2) less opioid-induced nausea, and (3) greater potential for physical dependency. This greater liability for physical dependence is the reason that heroin is not available legally for clinical use in the United States.^{192,193}

Opioid Agonist-Antagonists

Opioid agonist-antagonist drugs were touted in the 1970s and 1980s as analgesics that had none of the liability of full agonist opioids. Opioid agonist-antagonists used included pentazocine, butorphanol, nalbuphine, buprenorphine, nalorphine, bremazocine, and dezocine (**Figure 7.21**). As found previously and since, these claims did not hold up. The drugs bind to μ receptors, where they produce responses limited by a ceiling (partial agonists) or no effect (competitive antagonists). In addition, these drugs often exert partial agonist actions at other receptors, including α and δ receptors.¹⁹⁴ Antagonist properties of these drugs can attenuate the efficacy of subsequently administered opioid agonists and can induce profound symptoms of withdrawal when administered to patients who are currently treated with full agonist opioids. The side effects are similar to those of opioid agonists, and, in addition, these drugs may cause dysphoric reactions that largely limit their use in clinical practice. Only pentazocine, nalbuphine, butorphanol, and buprenorphine are used clinically to any degree.

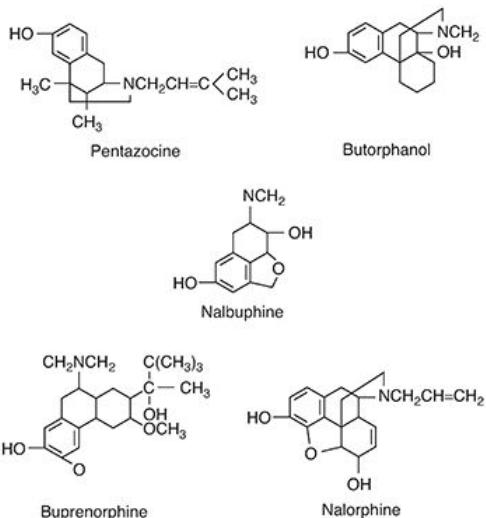


FIGURE 7.21 Opioid agonist-antagonists.

Pentazocine

Pentazocine is a benzomorphan derivative that possesses opioid agonist actions as well as weak antagonist activity. It is presumed to exert its analgesic effects through activation of δ and α receptors. Pentazocine is well absorbed after oral or parenteral administration. First-pass hepatic metabolism is extensive, with only about 20% of an oral dose entering the circulation. Metabolism occurs by oxidation of terminal methyl groups, and resulting inactive glucuronide conjugates are excreted in the urine. The elimination half-time is 2 to 3 hours.

Clinical Uses

Pentazocine, 10 to 30 mg IV or 50 mg orally, can be used for the relief of moderate pain. An oral dose of 50 mg is equivalent in analgesic effect to 60 mg of codeine. Pentazocine is useful for treatment of chronic pain when there is a high risk of physical dependence.

Side Effects

The most common side effect of pentazocine is sedation, followed by diaphoresis and dizziness. Dysphoria, including fear of impending death, is associated with high doses. Pentazocine produces an increase in the plasma concentrations of catecholamines, which may account for increases in heart rate, systemic blood pressure, pulmonary artery blood pressure, and left ventricular end-diastolic pressure that accompany administration of this drug.

Butorphanol

Butorphanol is an agonist-antagonist opioid that resembles pentazocine. Compared with pentazocine, its agonist effects are about 20 times greater, whereas its antagonist actions are 10 to 30 times greater.

Butorphanol has a low affinity for μ receptors to produce antagonism and moderate agonist activity at α receptors. It is used principally for treatment of migraine but is also effective to prevent shivering.

In postoperative patients, 2 to 3 mg IM produces analgesia and depression of ventilation similar to 10 mg of morphine. Intranasal butorphanol has been used for the treatment of postoperative pain and migraine pain. The intraoperative use of butorphanol, like pentazocine, seems to be limited. The elimination half-time of butorphanol is 2.5 to 3.5 hours. Metabolism is principally to inactive hydroxybutorphanol, which is eliminated largely in the bile and to a lesser extent in the urine.

Side Effects

Common side effects of butorphanol include sedation, nausea, and diaphoresis. Dysphoria, reported frequently with other opioid agonist-antagonists, is infrequent after administration of butorphanol. Depression of ventilation is similar to that produced by similar doses of morphine. Like pentazocine, analgesic doses of butorphanol increase systemic blood pressure, pulmonary artery blood pressure, and cardiac output. Also, similar to pentazocine, the effects of butorphanol on the biliary and gastrointestinal tract seem to be milder than those produced by morphine. It may be difficult to use an opioid agonist effectively as an analgesic in the presence of butorphanol.

Nalbuphine

Nalbuphine is an agonist-antagonist opioid that is related chemically to oxymorphone and naloxone. Nalbuphine is metabolized in the liver and has an elimination half-time of 3 to 6 hours. Naloxone reverses the agonist effects of nalbuphine. Nalbuphine is most commonly used to prevent shivering. Depression of ventilation is similar to that of morphine until 30 mg IM of nalbuphine is exceeded, after which no further depression of ventilation occurs (ceiling effect).¹⁹⁵

Buprenorphine

Buprenorphine is an agonist-antagonist opioid derived from the opium alkaloid thebaine. It is an old drug first introduced in the 1970s in a form. It is now available in multiple forms including transdermal, transmucosal, and subcutaneous that are used both for chronic pain and to prevent relapse in recovery from opioid abuse but is also effective in treating moderate to severe pain.¹⁹⁶ Its pharmacokinetics are unique in that it undergoes extensive first-pass metabolism and thus has little oral bioavailability. Absorption of its sublingual form that is commonly used to treat addiction ranges from 40 minutes to 3.5 hours. It is estimated that the affinity of buprenorphine for μ receptors is 50 times greater than that of morphine, and subsequent slow dissociation from these receptors accounts for its prolonged duration of action and resistance to antagonism with naloxone. The only clinically used opioid that has higher affinity of the μ receptor is sufentanil. The high affinity for the μ receptor and slow dissociation poses difficulty when a full agonist opioid is required for severe pain; for example, after surgery. There is debate on whether buprenorphine should be converted to a full agonist opioid before elective surgery. There are many excellent reviews available for more detailed discussion.^{197,198}

Side Effects

The side effects of buprenorphine include drowsiness, nausea, vomiting, and depression of ventilation. These are similar in magnitude to the side effects of morphine but may be prolonged and resistant to antagonism with naloxone. Pulmonary edema has been observed after administration of buprenorphine.¹⁹⁹ Because of its antagonist properties, buprenorphine can precipitate withdrawal in patients who are physically dependent on morphine. Initiation of buprenorphine treatment (induction) in patients receiving long-term treatment with a full agonist for prevention of abuse can be dangerous and should only be done by a provider experienced in this process.

Opioid Antagonists

Minor changes in the structure of an opioid agonist can convert the drug into an opioid antagonist at one or more of the opioid receptor sites ([Figure 7.22](#)).²⁰⁰ The most common change is substitution of an alkyl group for a methyl group on an opioid agonist. For example, naloxone is the *N*-alkyl derivative of oxymorphone (see [Figure 7.21](#)).

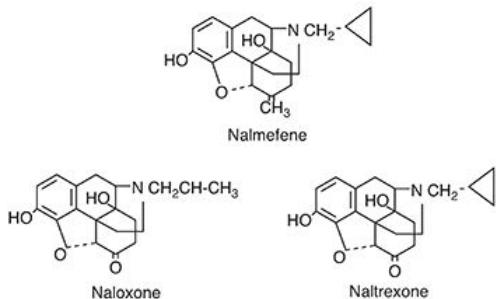


FIGURE 7.22 Opioid antagonists.

Naloxone and naltrexone are pure μ -opioid receptor antagonists with no agonist activity. The high affinity for opioid receptors characteristic of pure opioid antagonists results in displacement of the opioid agonist from μ receptors. After this displacement, the binding of the pure antagonist does not activate μ receptors and antagonism occurs. Nalmefene is an opioid antagonist primarily used for alcohol dependence and other addictions but could counteract full agonist opioids used for surgery.²⁰¹

Naloxone

Naloxone is a nonselective antagonist at all three opioid receptors. Naloxone is selective when used to (1) treat opioid-induced depression of ventilation as may be present in the postoperative period, (2) treat opioid-induced depression of ventilation in the neonate due to maternal administration of an opioid, (3) facilitate treatment of deliberate opioid overdose, and (4) detect suspected physical dependence. Naloxone, 1 to 4 $\mu\text{g}/\text{kg}$ IV, promptly reverses opioid-induced analgesia and depression of ventilation. Supplemental doses of naloxone will likely be necessary for sustained antagonism of opioid agonists. In this regard, a continuous infusion of naloxone, 5 $\mu\text{g}/\text{kg}/\text{hour}$, prevents depression of ventilation without altering analgesia produced by neuraxial opioids.²⁰² Higher doses may be needed to treat overdose with high-dose synthetic opioids. It is available in multiple forms including a nasal spray that can be administered by a first responder or bystander to an unconscious person suspected of opioid overdose.

Naloxone is metabolized primarily in the liver by conjugation with glucuronic acid to form naloxone-3-glucuronide. The elimination half-time is 60 to 90 minutes. Naloxone is absorbed orally, but metabolism during its first pass through the liver renders it only one-fifth as potent as when administered parenterally.

Side Effects

Antagonism of opioid-induced depression of ventilation is accompanied by an inevitable reversal of analgesia. It may be possible, however, to titrate the dose of naloxone such that depression of ventilation is partially but acceptably antagonized to also maintain partial analgesia.

Nausea and vomiting appear to be closely related to the dose and speed of injection of naloxone. Administration of naloxone slowly over 2 to 3 minutes rather than as a bolus seems to decrease the incidence of nausea and vomiting. Awakening occurs either before or simultaneously with vomiting, which ensures that the patient's protective upper airway reflexes have returned and the likelihood of pulmonary aspiration is minimized.

Cardiovascular stimulation after administration of naloxone manifests as increased sympathetic nervous system activity, presumably reflecting the abrupt reversal of analgesia and the sudden perception of pain. This increased sympathetic nervous system activity may manifest as tachycardia, hypertension, pulmonary edema, and cardiac dysrhythmias.²⁰³ Even ventricular fibrillation has occurred after the IV administration of naloxone and the associated sudden increase in sympathetic nervous system activity.²⁰⁴

Naloxone can easily cross the placenta. For this reason, administration of naloxone to an opioid-dependent parturient may produce acute withdrawal in the neonate.

Role in Treatment of Shock

Naloxone produces dose-related improvement in myocardial contractility and survival in animals subjected to hypovolemic shock and, to a lesser extent, in those subjected to septic shock.²⁰⁵ The beneficial effects of naloxone in the treatment of shock occur only with doses >1 mg/kg IV, suggesting that the beneficial effects of this drug are not opioid receptor mediated or, alternatively, are mediated by opioid receptors other than μ receptors—possibly δ and α receptors.

Antagonism of General Anesthesia

The occasional observation that high doses of naloxone seem to antagonize the depressant effect of inhaled anesthetics may represent drug-induced activation of the cholinergic arousal system in the brain, independent of any interaction with opioid receptors.²⁰⁶ A role of endorphins in the production of general anesthesia is not supported by data demonstrating a failure of naloxone to alter anesthetic requirements (MAC) in animals.

Naltrexone

Naltrexone, in contrast to naloxone, is highly effective orally, producing sustained antagonism of the effects of opioid agonists for as long as 24 hours. It has found a role in the treatment of alcoholism, possibly by reducing the pleasure associated with ethanol intoxication.²⁰⁷ It is also used at ultralow doses for chronic pain, thought to be mediated by activity at μ receptors on microglia.

Methylnaltrexone

Methylnaltrexone ([Figure 7.23](#)) is a quaternary opioid receptor antagonist. The highly ionized quaternary methyl group limits the transfer of methylnaltrexone across the blood–brain barrier. As a result, methylnaltrexone is active at peripheral rather than central opioid receptors as demonstrated by its failure to penetrate the CNS sufficiently to promote withdrawal in morphine-dependent animals.

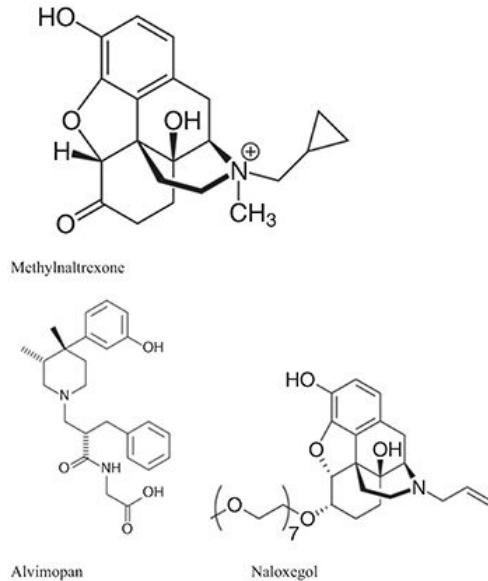


FIGURE 7.23 Chemical structure of methylnaltrexone, alvimopan, and naloxegol—oral peripheral opioid antagonists.

In humans, methylnaltrexone attenuates morphine-induced changes in the rate of gastric emptying and also decreases the incidence of nausea.²⁰⁸ The attenuation of morphine-induced nausea may be due to antagonism of morphine at the chemoreceptor trigger zone (located outside the blood–brain barrier) or through limitation of the delay in gastric emptying, which, in itself, may cause nausea. Presumably, methylnaltrexone could prevent the undesirable effects of opioids on gastric emptying and possibly vomiting without altering centrally mediated analgesia.

Alvimopan

Alvimopan (see [Figure 7.23](#)) is a μ -selective oral peripheral opioid antagonist. Its oral bioavailability is approximately 6%, and its metabolism also relies on gut flora.²⁰⁹ It was approved by the US Food and Drug Administration for treatment of postoperative ileus and has shown mixed results in subsequent clinical trials for treating ileus or opioid-induced constipation. Although likely safe in the acute setting, there is concern about a potential increase in cardiovascular events with long-term use.²¹⁰ It is, however, a component of many “enhanced recovery” programs designed to reduce the duration of hospitalization after surgery.²¹¹

Naloxegol

Naloxegol (see [Figure 7.23](#)) is another peripherally acting μ -opioid receptor antagonist. It is a polyethylene glycosylated derivative of naloxone. It was originally classified as a schedule II drug (high abuse potential) in the United States because it can be derived from opium alkaloids. However, it was subsequently reclassified as a class V prescription drug.²¹² It is approved for treatment of opioid-induced constipation in chronic pain states. The drug is rapidly absorbed after oral administration with principally hepatic elimination.²¹³

Tamper- or Abuse-Resistant Opioids

In recent years, prescribing of opioids for chronic noncancer pain has gained greater social acceptance, although this has led to significant consequences (see “[The ‘Opioid Crisis’](#)”). Along with this increase in prescription use, there has been a dramatic rise in drug diversion and abuse, both of which have a significant human and economic cost.²¹⁴

In an attempt to provide effective oral opioid analgesia with less potential for abuse, oral opioid formulations have been developed to reduce the ability to rapidly ingest the active ingredient (crushing, snorting, injecting) with subsequent euphoric effects.²¹⁵ One strategy involves combining the opioid with an antagonist. Examples of this strategy include Suboxone (buprenorphine plus naloxone), Embeda (extended-release morphine plus naltrexone), and OxyNal (oxycodone plus naltrexone). A second approach involves combining the opioid with a substance that becomes gelatinous when mixed for illicit injection, thus hampering improper use. Convincing evidence on these strategies’ efficacy is currently lacking, but they may prove to fill a useful role in chronic oral analgesic use by preventing opioid overdose due to crushing or injecting the extended-release opioid formulation.

Opioid Allergy

Although many patients claim “allergies” to opioids, true opioid allergy is rare. More often, predictable side effects of opioids such as localized histamine release, orthostatic hypotension, nausea, and vomiting are misinterpreted as an allergic reaction. Patients frequently perceive side effects as “allergy.” Morphine contains a tertiary amine group that causes nonimmune release of histamine. True allergic reactions to morphine are much rarer. Fentanyl is chemically dissimilar to morphine and, as such, does not cross-react with morphine derivatives.²¹⁶

Opioid Immune Modulation

Opioid therapy may alter immunity through neuroendocrine effects or via direct effects on the immune system.^{44,217} Opioid receptors are present on immune cells, including T- and B-lymphocytes, dendritic cells, neutrophils, macrophages, and microglia.⁴⁵ Prolonged exposure to opioids appears more likely than short-term exposure to produce immunosuppression especially in susceptible persons.

Of recent interest is the possible link between opioid-induced immunosuppression and cancer recurrence after resection.^{218–221} Opioids alter the development, differentiation, and function of immune cells and particularly seem to depress natural killer cell activity ([Figure 7.24](#)).^{222–224} Natural killer cells are lymphoid lineage cells that induce apoptosis in target cells via mechanisms distinct from T-lymphocytes and appear to be a major factor in tumor surveillance. Although immunosuppressant effects of opioids raise concerns, it is equally important to recognize that pain itself can impair immune function.

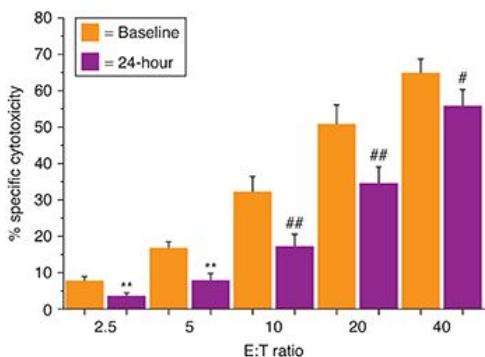


FIGURE 7.24 Depressed peripheral blood natural killer cell cytotoxicity immediately after a 24-hour high-dose morphine infusion in nine participants. Values are percentage-specific cytotoxicity at each effector-target (E:T) ratio tested (mean \pm standard error). **, $P < .05$ versus baseline value; ##, $P < .005$ versus baseline value; #, $P < .01$ versus baseline value. Reprinted with permission from Yeager MP, Colacchio TA, Yu CT, et al. Morphine inhibits spontaneous and cytokine-enhanced natural killer cell cytotoxicity in volunteers. Anesthesiology. 1995;83(3):500-508. Copyright © 1995 American Society of Anesthesiologists, Inc.

Anesthetic Requirements

The contribution of opioids to total anesthetic requirements can be estimated by determining the decrease in MAC of a volatile anesthetic in the presence of opioids. In animals, morphine decreases the MAC of volatile anesthetics in a dose-dependent manner, but there appears to be a ceiling effect to the anesthetic-sparing ability of morphine, with a plateau at 65% MAC.²²⁵ A single dose of fentanyl, 3 μ g/kg IV 25 to 30 minutes before surgical incision, decreases isoflurane or desflurane MAC by about 50%.²²⁶ In patients, a sufentanil plasma concentration of 0.145 ng/mL produced a 50% decrease in isoflurane MAC, whereas plasma sufentanil concentrations of >0.5 ng/mL exhibited a ceiling effect.^{227,228} The decrease in MAC produced by remifentanil is similar to that produced by other opioids and ranges from 50% to 91%, depending on the plasma concentration of remifentanil.²²⁹ These data cast serious doubt on the ability of opioid agonists to provide reliable amnesia during surgical procedures, even at extremely high doses.

Opioid agonist-antagonists are less effective than opioid agonists in decreasing MAC. For example, butorphanol, nalbuphine, and pentazocine maximally decrease MAC 11%, 8%, and 20%, respectively, even when the dose of these drugs is increased 40-fold.²³⁰ The ceiling effect for MAC parallels the ceiling effect for depression of ventilation and is consistent with the clinical impression that even large doses of opioid agonist-antagonists do not produce unconsciousness or even prevent patient movement in response to painful stimulation. Thus, the intraoperative role for these drugs is minimal and limits the effectiveness of full agonist opioids.

Patient-Controlled Analgesia

As an alternative to intermittent bolus dosing of medication, patients may be provided with a mechanism to address their own analgesic requirements. Termed **patient-controlled analgesia**, this most typically involves a programmable electronic pump that delivers a prescribed dose of medication upon patient demand. The rationale of this technique is that, by using frequent, small doses of opioid, patients will have better control of their pain by keeping effect site concentrations in the therapeutic range for a larger proportion of the time. Rather than wide swings between inadequate analgesia and oversedation, the PCA regimen is designed to allow patients to self-titrate their dosing to optimize their pain management ([Figure 7.25](#)).

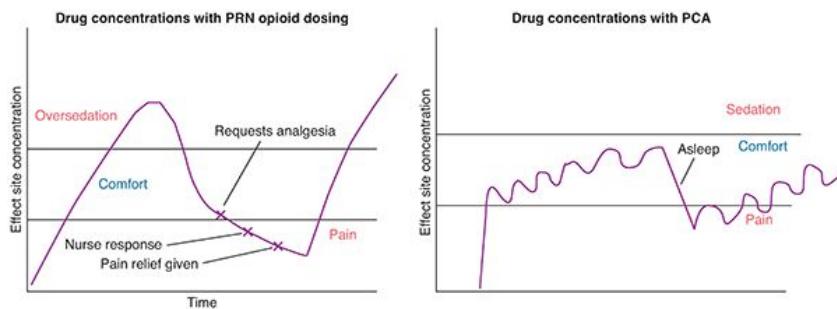


FIGURE 7.25 Effect site concentrations with traditional versus patient-controlled opioid dosing. After achieving effective concentrations, patient-controlled analgesia (PCA) allows patients to self-titrate opioid dosing to maintain effective analgesia.

Proposed advantages of this technique include decreased health care provider workload, increased patient satisfaction, lower opioid consumption, and the inherent safety of needing a conscious patient to self-administer a dose of opioid.²³¹ Despite multiple studies, PCA only provides marginally improved analgesia over conventional opioid therapy. Patient satisfaction, however, is significantly higher with PCA.²³² Typically, PCA uses IV opioids. Morphine, hydromorphone, and fentanyl are the most common choices. Suggested initial dosing regimens are listed in [Table 7.5](#).

TABLE 7.5

Suggested starting intravenous patient-controlled analgesia opioid regimens

Drug	Basal rate ^a	Bolus dose	Bolus interval (minutes)
Morphine	0-2 mg/hour	1-2 mg	6-10
Hydromorphone	0-0.4 mg/hour	0.2-0.4 mg	6-10
Fentanyl	0-60 µg/hour	20-50 µg	5-10

^aBasal infusions are not typically recommended for opioid-naïve patients.

Owing to the unique pharmacokinetic profile of remifentanil, it has found a role in PCA for labor and delivery. Because remifentanil undergoes nonenzymatic hydrolysis in both the maternal and fetal circulations, and is extensively metabolized in the placenta, it has minimal effects on the neonate. The mother must be carefully monitored as the rapid increase in plasma concentration can cause acute respiratory depression. In cases where epidural analgesia is contraindicated, remifentanil PCA has proven to be a viable but not fully efficacious alternative during the first stage of labor.²³³ It is more effective for patient satisfaction than for contemporaneous pain report.²³⁴

Neuraxial Opioids

Placement of opioids in the epidural or subarachnoid space to manage acute or chronic pain is based on the knowledge that opioid receptors (principally μ receptors) are present in the substantia gelatinosa of the spinal cord.²³⁵ Analgesia produced by neuraxial opioids, in contrast to regional anesthesia with local anesthetics, is not associated with sympathectomy, sensory block, or motor block. Analgesia is dose related (epidural dose is 5-10 times the subarachnoid dose) and effective for visceral pain. Neuraxial morphine may decrease the MAC for volatile anesthetics, although not all investigators have demonstrated this effect.²³⁶⁻²³⁸

Analgesia that follows epidural placement of opioids reflects diffusion of the drug across the dura to gain access to μ -opioid receptors in the spinal cord as well as systemic absorption to produce effects similar to those that would follow IV administration of the opioid. For example, the mechanism of postoperative analgesia produced by epidural administration of highly lipophilic opioids (fentanyl, sufentanil) may be primarily a reflection of systemic absorption, but this has been refuted.^{239,240} Poorly lipid-soluble opioids such as morphine result in a slower onset of analgesia but a longer duration of action than lipid-soluble opioids when administered via the neuraxial route.

Pharmacokinetics

Opioids placed in the epidural space may undergo uptake into epidural fat, systemic absorption, or diffusion across the dura into the CSF.²⁴¹ Epidural administration of opioids produces considerable CSF concentrations of drug. Penetration of the dura is highly influenced by lipid solubility, but molecular weight may also be important. Fentanyl and sufentanil are, respectively, approximately 800 and 1,600 times as lipid soluble as morphine. After epidural administration, CSF concentrations of fentanyl peak in about 20 minutes and sufentanil in about 6 minutes. In contrast, CSF concentrations of morphine, after epidural administration, peak in 1 to 4 hours. Furthermore, only about 3% of the dose of morphine administered epidurally crosses the dura to enter the CSF.²⁴²

The epidural space contains an extensive venous plexus, and vascular absorption of opioids from the epidural space is extensive. After epidural administration, fentanyl blood concentrations peak in 5 to 10 minutes, whereas blood concentrations of the more lipid-soluble sufentanil peak even sooner.²⁴³ In contrast, blood concentrations of morphine after epidural administration peak after 10 to 15 minutes. Epidural administration of morphine, fentanyl, and sufentanil produces opioid blood concentrations that are similar to those produced by an IM injection of an equivalent dose.²⁴¹ The addition of epinephrine to the solution placed into the epidural space decreases systemic absorption of the opioid but does not influence the diffusion of morphine across the dura into the CSF. The addition of epinephrine to intrathecal morphine solutions enhances postoperative analgesia compared with intrathecal morphine alone.²⁴⁴ Vascular absorption after intrathecal administration of opioids is clinically insignificant.

Cephalad movement of opioids in the CSF principally depends on lipid solubility. For example, lipid-soluble opioids such as fentanyl and sufentanil are limited in their cephalad migration by uptake into the spinal cord, whereas less lipid-soluble morphine remains in the CSF for transfer to more cephalad locations. After lumbar intrathecal morphine administration, appreciable cervical CSF concentrations occur 1 to 5 hours after injection, whereas cervical CSF concentrations of highly lipid-soluble opioids are minimal after their epidural administration. The underlying cause of ascension of morphine is bulk flow of CSF. CSF ascends in a cephalad direction from the lumbar region, reaching the cisterna magna in 1 to 2 hours and the fourth and lateral ventricles by 3 to 6 hours.²⁴¹ Coughing or straining, but not body position, can affect movement of CSF. The elimination half-time of morphine in CSF is similar to that in plasma.²⁴⁵

Side Effects

Side effects of neuraxial opioids are caused by the presence of drug in either the CSF or systemic circulation.²⁴¹ In general, most side effects are dose dependent. Some side effects are mediated via interaction with specific opioid receptors, whereas others are nonspecific. Side effects are less common in patients chronically exposed to opioids. The four classic side effects of neuraxial opioids are pruritus, nausea and vomiting, urinary retention, and depression of ventilation.

Pruritus

Pruritus is the most common side effect with neuraxial opioids. It may be generalized but is more likely to be localized to the face, neck, or upper thorax. The incidence of pruritus varies widely and is often elicited only after direct questioning. Severe pruritus is rare, occurring in about 1% of patients. Pruritus is more likely to occur in obstetric patients, perhaps due to the interaction of estrogen with opioid receptors. The incidence may or may not be dose related. Pruritus usually occurs within a few hours of injection and may precede the onset of analgesia.

Pruritus induced by neuraxial opioids is likely due to cephalad migration of the opioid in CSF and subsequent interaction with opioid receptors in the trigeminal nucleus. An opioid antagonist such as naloxone is effective in relieving opioid-induced pruritus. Antihistamines may be an effective treatment for pruritus, but this is likely secondary to their sedative effect.

Urinary Retention

Urinary retention with neuraxial opioids is more common than after IV or IM administration of equivalent doses of the opioid. The incidence of this side effect is not dose dependent or related to systemic absorption of the opioid. Urinary retention is most likely due to interaction of the opioid with opioid receptors located in the sacral spinal cord. This interaction promotes inhibition of sacral parasympathetic nervous system outflow, which causes detrusor muscle relaxation and an increase in maximum bladder capacity, leading to urinary retention. In humans, epidural morphine causes marked detrusor muscle relaxation within 15 minutes of injection that persists for up to 16 hours; it is readily reversed with naloxone.²⁰²

Depression of Ventilation

The most serious side effect of neuraxial opioids is depression of ventilation, which may occur within minutes of administration or may be delayed for hours.

Early depression of ventilation occurs within 2 hours of neuraxial injection of the opioid. Most reports of clinically important depression of ventilation involve epidural administration of fentanyl or sufentanil. This depression of ventilation may result from systemic absorption of the lipid-soluble opioid, although cephalad migration of opioid in the CSF may also be responsible. Clinically significant early depression of ventilation after intrathecal injection of morphine is unlikely.

Delayed depression of ventilation occurs more than 2 hours after neuraxial opioid administration and reflects cephalad migration of the opioid in the CSF and subsequent interaction with opioid receptors located in the ventral medulla. All reports of clinically significant delayed depression of ventilation involve morphine.²⁴¹ Delayed depression of ventilation characteristically occurs 6 to 12 hours after epidural or intrathecal administration of morphine. Clinically important depression of ventilation has not been described more than 24 hours after the epidural or intrathecal injection of morphine.

Factors that increase the risk of delayed depression of ventilation, especially concomitant use of any IV opioid or sedative, must be considered in determining the dose of neuraxial opioid (see **Table 7.3**).²⁴¹ Coughing may affect the movement of CSF and increase the likelihood of depression of ventilation. Obstetric patients appear to be at less risk for severe ventilatory depression.²⁴⁶

Detection of depression of ventilation induced by neuraxial opioids may be difficult. Arterial hypoxemia and hypercarbia may develop despite a normal breathing rate (**Figure 7.26**).²⁴⁷ Pulse oximetry reliably detects opioid-induced arterial hypoxemia, and supplemental oxygen (2 L/min) is an effective treatment for hypoxia but may mask hypercarbia. Supplemental oxygen, however, can mask significant hypoventilation. The most reliable clinical sign of depression of ventilation, however, appears to be a depressed level of consciousness, possibly caused by hypercarbia; however, this is a very undesirable late sign.²⁴¹ In patients receiving supplemental oxygen, arterial hypoxemia is a very late sign of hypoventilation; thus, pulse oximetry is of limited value in detection of opioid-induced respiratory depression in these patients. Continuous respiratory rate or carbon dioxide monitoring may be indicated in some settings. Prophylactic infusions of naloxone are of variable efficacy in protecting against depression of ventilation.^{202,248} Naloxone (0.25 µg/kg/hour IV) is effective in attenuating the side effects (nausea and vomiting, pruritus) associated with morphine-induced analgesia delivered by a patient-controlled IV delivery system.²⁴⁹

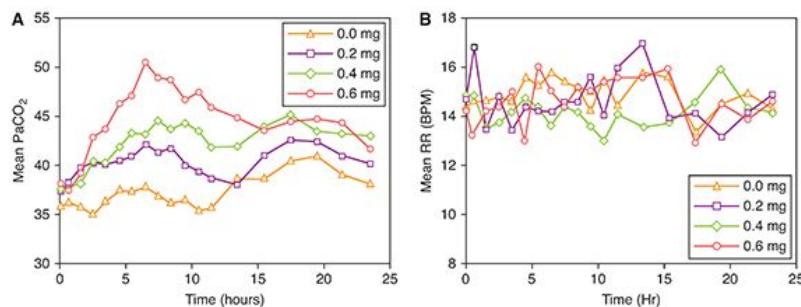


FIGURE 7.26 Mean PaCO_2 (mm Hg) (A) and mean respiratory rate (RR) (B) versus times before (time 0) and after three different doses of intrathecal morphine. Reprinted with permission from Bailey PL, Rhondeau

S, Schafer PG, et al. Dose-response pharmacology of intrathecal morphine in human volunteers. Anesthesiology. 1993;79(1):49-59. Copyright © 1993 American Society of Anesthesiologists, Inc.

Sedation

When sedation occurs with neuraxial opioids, depression of ventilation must be considered. Mental status changes other than sedation may also occur with neuraxial opioids. Naloxone-reversible psychosis, catatonia, and hallucinations have been described.²⁴¹

Central Nervous System Excitation

Tonic skeletal muscle rigidity resembling seizure activity is a well-known side effect of large IV doses of opioids, but this response is rarely observed after neuraxial administration. Myoclonic activity has been observed after neuraxial opioids and, in one report, progressed to a grand mal seizure.²⁵⁰ Although large doses of opioids reliably produce seizures in animals, clinically relevant doses of IV or neuraxial opioids are unlikely to be associated with generalized cortical seizure activity in humans.²⁴¹ Cephalad migration of the opioid in CSF and subsequent interaction with nonopioid receptors in the brainstem or basal ganglia is the most likely explanation for opioid-induced CNS excitation. In this regard, opioids may block glycine or γ -aminobutyric acid-mediated inhibition.

Viral Reactivation

A link exists between the use of epidural morphine in obstetric patients and reactivation of herpes simplex labialis virus. Reactivation of the herpes virus occurs 2 to 5 days after epidural administration of the opioid.²⁵¹ Manifestation of symptoms of herpes labialis (cold sores) characteristically occurs in the same sensory innervation as the primary infection, which are usually facial areas innervated by the trigeminal nerve. The underlying mechanism causing herpes virus reactivation likely involves cephalad migration of opioid in CSF and subsequent interaction with the trigeminal nucleus.

Neonatal Morbidity

Systemic absorption after epidural administration of an opioid results in predictable blood levels of the drug in the neonate immediately after birth. Clinically important depression of ventilation has been observed in the newborns of mothers receiving epidural opioids.²⁴¹ The progress of labor in general does not seem to be adversely affected by neuraxial opioids.²⁵² After administration of epidural fentanyl or sufentanil to parturients, the concentration of opioid in breast milk is negligible.⁴¹ As a general rule, systemic or neuraxial opioid analgesics should not be withheld from women recovering from cesarean delivery due to concerns of neonatal drug exposure in breast milk.

Miscellaneous Side Effects

Epidural morphine has been associated with sustained erection (priapism) and inability to ejaculate.²⁵³ Naloxone-reversible miosis, nystagmus, and vertigo may occur after neuraxial opioids, most commonly morphine. Neuraxial opioids may delay gastric emptying, most likely reflecting an interaction of the opioid with a spinal cord opioid receptor.²⁵⁴ Neuraxial opioids, by inhibiting shivering, may cause decreased body temperature. Neuraxial opioids have been implicated as possible causes of spinal cord damage, especially following accidental use of opioids containing toxic preservatives.²⁴¹ Clinical manifestations in these patients include sensory and motor neurologic dysfunction, myoclonic spasms, paresis, and paralysis. On the other hand, neuraxial opioids have been administered chronically without adverse sequelae.

Opioid Safety Issues

Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is a clinical syndrome characterized by recurrent episodes of apnea or hypopnea due to upper airway collapse during sleep. Due to their effects on ventilation, opioids pose a particular risk to this population. Additionally, individuals with OSA demonstrate an increased sensitivity to

the respiratory depressant effects of opioids. Many society guidelines on perioperative management of these patients exist,^{255,256} but strong supporting evidence is often lacking.²⁵⁷ General recommendations include minimizing the amount of opioid administered (such as by using multimodal and/or regional analgesia) and carefully evaluating the appropriateness of patients for ambulatory surgery. The first postoperative day appears to be the time of highest risk for opioid-induced respiratory depression, although the exacerbation of patients' OSA severity may peak on the third postoperative night and persist for up to 7 days.²⁵⁸

Practical Issues

A majority of patients prescribed oral opioids do not consume the entire prescription, and many of these prescriptions are not disposed of.²⁵⁹ Improperly stored opioids pose a safety hazard and provide a large opportunity for diversion.²⁶⁰ Thus, proper storage and disposal of prescribed opioids are a simple way to prevent harm. Although package inserts often contain detailed instructions for proper storage and disposal, education efforts for patients are still needed.²⁶¹

The “Opioid Crisis”

Opioids have always posed a public health risk due to their potential for abuse. In recent years, however, the United States has seen a surge in opioid prescribing, diversion, and overdose deaths. Starting in the early 2000s, regulatory and accreditation bodies pushed the measurement of pain as a “fifth vital sign.” Prescription of opioids increased rapidly. Diversion and abuse also increased, with over 33,000 reported opioid (legal and illicit) overdose deaths in 2015.²⁶² Opioid prescribing for acute and/or chronic pain now serves as a gateway for the illicit use of heroin, as it is often less expensive than diverted opioid medications.²⁶³ Potent synthetic opioids such as fentanyl are used illicitly and may also be unwittingly consumed when heroin is “cut” with synthetic opioids, thus contributing to overdose deaths.²⁶⁴ In addition to the human cost, the financial burden to society is enormous, estimated at US \$72.5 billion annually.²⁶⁵ Multiple means of controlling this epidemic have been proposed and/or instituted, including prescription drug monitoring programs, patient education, media coverage, state medical board actions, lawsuits against pharmaceutical companies, and comprehensive prescriber education efforts.²⁶⁶ The appropriate management of patients with pain, however, often still legitimately requires consideration of the risks and the benefits and the rational inclusion of opioids as part of a comprehensive pain management plan.²⁶⁷

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Centrally Acting Nonopioid Analgesics*

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Opioid drugs are widely used drugs for the management of both acute and chronic pain. Side effects of opioids may limit their use, and concerns over drug dependence, misuse, and abuse have recently broadened boundaries on their use. The Centers for Disease Control and Prevention and the Agency for Healthcare Research and Quality have reported that evidence supporting the effectiveness of opioids for most non-cancer-related chronic pain syndromes is limited.^{1,2} This finding is not unexpected given our admittedly incomplete knowledge of physiology. Transition from acute to chronic pain involves release of inflammatory mediators and activation of microglia and changes protein expression in the dorsal horn.³ These complex changes may explain the decreased of opioids when pain transitions from acute to chronic.⁴ Chronic opioid administration induces microglial activation and the release of proinflammatory cytokines and chemokines.^{5,6} Inhibiting microglial activation mitigates the development of tolerance and opioid-induced reward mechanism^{7,8} and restores the analgesic efficacy of opioids.⁹ There are several nonopiate centrally administered analgesics that are supported for the treatment of in the literature.¹⁰ Nonnarcotic medication and treatments forming the base of multimodal analgesia is important to reducing reliance on opioids. Relieve pain by mechanisms mainly unrelated to opioid receptors reduces the risk of respiratory depression, physical dependence, and abuse.

In order to minimize the adverse effects of opioid analgesic medications, anesthesiologists and surgeons are increasingly turning to nonopioid analgesic techniques as adjuvants for managing pain during the perioperative period. Neuraxial drug administration describes techniques that deliver drugs in close proximity to the spinal cord, that is, intrathecally into the cerebrospinal fluid or epidurally into the fatty tissues surrounding the dura, by single injection or continuous infusion through a catheter. The administration of centrally acting agents bypasses the blood-brain barrier resulting in a higher cerebrospinal fluid concentration allowing using reduced amounts of medication to achieve equipotent doses.

The addition of neuraxial nonopioid adjuvants to local anesthetic may improve the quality of analgesia. Nonopioid neuraxial adjuvants have different mechanisms of actions and thus often have additive or synergistic effects. Potential advantages include a reduction in dose of individual drugs and a reduction in opioid requirement for rescue. Neuraxial administration of medications confers an inherent risk of injury to structures of the nervous system, not only by the needles and catheters used but also by neurotoxic effects of the compounds injected. Therefore, the potential neurotoxicity of any drug used in this setting needs careful study and validation before human use.¹¹

It is important to note that the US Food and Drug Administration (FDA) has not approved neuraxial (epidural or subarachnoid) administration of some of the drugs listed in this chapter for use clinically. Any drug considered for intrathecal administration in humans requires histologic, physiologic, and behavioral testing in a number of animal species before being considered for clinical use. Most drugs have not been sufficiently well studied to recommend their neuraxial use. Many drug preparations also contain antioxidants, preservatives, and excipients, which might contribute to neurotoxicity. In previous years, many drugs were tested in the neuroaxis without the required preclinical studies. Currently, many journals will not accept clinical trials of neuraxial drugs without preclinical toxicology and proper regulatory approval for the studies.

α_2 -Adrenergic Agonists

Epidural and intrathecal administration of α_2 -adrenergic agonists provide analgesia by activating α_2 -adrenergic receptors (G protein-coupled inhibitory receptors) on the sympathetic preganglionic neurons that mediate a reduction in norepinephrine (NE) release (via a negative feedback mechanism). Descending

noradrenergic pathways, originating in nuclei A₅ and A₇ in the pons and midbrain, appear to play a major inhibitory role on sympathetic preganglionic neuron activity.¹² The overall effect is sympatholysis resulting in analgesia, hypotension, bradycardia, and sedation.^{13,14}

Clonidine

Clonidine acts as a selective partial agonist of the α₂ receptors. It inhibits nociceptive impulse at postjunctional α₂ receptors in the dorsal horn of spinal cord. Neuraxial clonidine has been shown to be an effective analgesic for chronic cancer and noncancer pain as well as for postoperative pain. Clonidine has antihypertensive effects, and it has been shown to potentiate postoperative analgesia induced by local anesthetics. Spinal clonidine causes a 30% prolongation of sensory and motor block of local anesthetics. Clonidine is commonly administered epidurally in doses ranging from 75 to 150 μg. The doses used for intrathecal (spinal) analgesia ranges from 15 to 40 μg. For caudal analgesia, clonidine is administered as 1 μg/kg dose.

Intrathecal administration of clonidine 37.5 to 150 μg with bupivacaine results in a dose-dependent increase in sensory blockade and more pain-free intervals in the postoperative period. An intrathecal dose of 150 μg was noted to be associated with motor blockade.¹⁴ With combined spinal epidural anesthesia, the intrathecal clonidine doses as low as 15 μg resulted in an increased duration of anesthesia, analgesia, and motor blockade.

Epidural clonidine in the postoperative period reduced visual analog scale score and also decreased morphine consumption. Addition of clonidine intrathecally or epidurally was associated with significant reduction of heart rate and blood pressure.¹⁵ Epidural clonidine 1 μg/mL when added to morphine 0.1 mg/mL in 0.2% ropivacaine significantly reduced postoperative pain scores of total knee arthroplasty patients.

Neuraxially administered opioids and α₂ agonists exhibit synergism.¹³ The addition of clonidine to opioids for postoperative analgesia as a continuous epidural infusion reduces opioid requirements by 20% to 60%.¹⁶ The addition of 75 μg clonidine to epidural ropivacaine results in longer and effective analgesia for cesarean delivery. Clonidine is a useful adjunct for labor epidural analgesia. It has been shown to reduce local anesthetic requirements and improve pain scores when combined with 0.125% bupivacaine with or without fentanyl 2 μg/mL. When used in a concentration of 1 to 2 μg/mL, clonidine has not been shown to have significant effects on fetal heart rate, Apgar scores, or umbilical cord gases. It may have additional beneficial effects in women with preeclampsia by stabilizing blood pressure.

Neuraxial clonidine is indicated for the treatment of intractable pain in cancer patients unresponsive to maximum doses of opioids. This formed the basis for the approval of epidural clonidine by the FDA.¹⁷ Its use as an adjunct has been most widely accepted in pediatric anesthesia, as a means of increasing the duration of analgesia from caudal block, and, to a lesser extent in obstetric anesthesia, to provide analgesia in labor.¹⁸ Clonidine carries a black box warning for neuraxial use in perioperative and obstetric anesthesia and analgesia. “Obstetrical, postpartum, or perioperative pain management: Clonidine hydrochloride injection (epidural clonidine) is not recommended for obstetrical, postpartum, or perioperative pain management. The risk of hemodynamic instability, especially hypotension and bradycardia, from epidural clonidine may be unacceptable in these patients. However, in a rare obstetrical, postpartum or perioperative patient, potential benefits may outweigh the possible risks.”

Intrathecal clonidine appears to have antihyperalgesic properties.^{13,18–21} As hyperalgesia is the physiologic expression of central nervous system (CNS) sensitization, it may be useful in preventing the increased risk of patients with severe postoperative pain and central sensitization from developing persistent, long-term, or chronic pain after surgery.²²

Recent systematic review aimed to quantify beneficial and harmful effects of clonidine when used as an adjuvant to intrathecal local anesthetics for surgery concluded that clonidine prolongs the regression of the sensory block in a dose-dependent manner, prolongs the time to the first request of an analgesic, and prolongs the duration of complete motor block, with weak evidence of dose responsiveness. In addition, clonidine decreases the risk of intraoperative pain and increases the risk of arterial hypotension, without evidence of

dose responsiveness. Finally, clonidine has no relevant impact on the time to achieve complete sensory or motor block, on the extent of the cephalad spread of the sensory block, or on the risk of bradycardia.²³

Dexmedetomidine

Dexmedetomidine has a higher affinity and is more selective for α_2 receptors than clonidine and is associated with a fewer hemodynamic and systemic side effects. Evidence indicates that neuraxial administration of dexmedetomidine produces spinal analgesia as efficiently as clonidine.²⁴⁻²⁶ A dose of 3 μg of intrathecal dexmedetomidine was found to be equipotent with 30 μg of clonidine.²⁷ Intrathecal dexmedetomidine 5 μg and fentanyl 25 μg were compared for vaginal surgeries with bupivacaine anesthesia. Dexmedetomidine caused significantly longer sensory and motor blockade.²⁸ In neuraxial and peripheral nerve blocks, dexmedetomidine exhibits synergism with local anesthetics prolonging sensory and motor block, delaying the time to the first analgesic, and improving postoperative analgesia.²⁹

Clinical studies exhibit potentiation of neuraxial local anesthetics, decrease in intraoperative anesthetic requirements with prevention of intraoperative awareness, and improved postoperative analgesia when epidural dexmedetomidine was used in conjunction with general anesthesia.^{17,24-26,30,31} The addition of 2 $\mu\text{g}/\text{kg}$ dexmedetomidine epidurally prolongs the duration of analgesia and decreases the requirement of rescue analgesics in patients undergoing lower limb orthopedic surgery, abdominal surgeries, and cesarean section albeit associated with a significant fall in heart rate and mean arterial blood pressure. In thoracic surgery, the use of epidural dexmedetomidine decreases the anesthetic requirements, prevents awareness during anesthesia, and improves intraoperative oxygenation and postoperative analgesia.³² Caudal dexmedetomidine in a dose of 2 $\mu\text{g}/\text{kg}$ with bupivacaine used in pediatric patients undergoing hernia repair or orchioepexy was found to cause more sedation, prolonged analgesia, less anesthetic consumption, and less irritability. There were no hemodynamic differences when compared to patients who had received only bupivacaine.³³⁻³⁵

No neurologic deficits have been reported till date in studies on both humans and animals during intrathecal or epidural administration of dexmedetomidine. However, there is some evidence of demyelination of the oligodendrocytes in the white matter, suggesting harmful effects on the myelin sheath when administered via the epidural route in animal studies. Advanced pathologic investigations in at least two animal species are required to establish the safety of dexmedetomidine for general clinical use. Nevertheless, the observed side effects of α_2 -adrenergic agonists are limited to hemodynamic effects (ie, bradycardia and hypotension).

Neostigmine

Neostigmine acts by inhibiting acetylcholinesterase enzyme and preventing the breakdown of acetylcholine. Naguib and Yaksh^{13,36} demonstrated that the intrathecal administration of cholinesterase inhibitors (neostigmine or edrophonium) produces a dose-dependent antinociceptive activity in rats (**Figure 8.1**). These antinociceptive effects are independent of opioid and α_2 -receptor systems and are primarily due to stimulation of muscarinic (but not nicotinic) cholinergic receptors. The use of intrathecal acetylcholinesterase inhibitors, such as neostigmine, result in analgesia in both preclinical and clinical models. Neostigmine is a hydrophilic molecule, like morphine, and when applied to the epidural space, it requires time to diffuse through dura mater into the subarachnoid space.^{37,38} Naguib and Yaksh^{13,36} noted in other studies that the side effects associated with intrathecal neostigmine in animals preclude its potential clinical utility as a sole analgesic. Unlike many adjuvants trialed in clinical studies, neostigmine toxicology was studied in two animal models, and the clinical trials were granted status as an investigational new drug by the FDA.³⁹

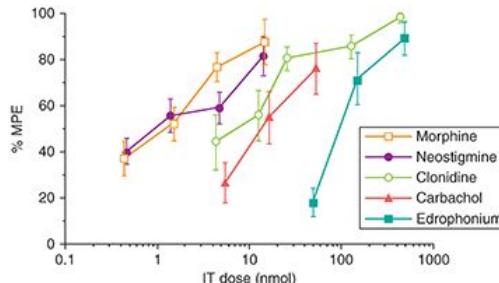


FIGURE 8.1 Log dose-response curves for the effects of intrathecally administered morphine, neostigmine, clonidine, carbachol, and edrophonium on the thermal nociceptive threshold. The response is presented as maximal possible effect (%MPE) versus log dose in nanomoles. Each point on the graph represents the mean \pm standard error of the mean. IT, intrathecal. *Reproduced from Naguib M, Yaksh TL. Antinociceptive effects of spinal cholinesterase inhibition and isobolographic analysis of the interaction with mu and alpha 2 receptor systems. Anesthesiology. 1994;80:1338-1348.*

Intrathecal neostigmine has been used as an adjunct to intrathecal local anesthetic and/or opioid to prolong regional analgesia and improve hemodynamic stability, with variable results. Escalating doses of intrathecal neostigmine (10-100 μ g) followed by 2% epidural lidocaine resulted in improved analgesia in a dose-independent manner after cesarean delivery.⁴⁰ The reduction in morphine requirements lasted up to 10 hours without adverse fetal effects, but the incidence of nausea varied from 50% to 100% in patients. In another study, intrathecal neostigmine (10 μ g) alone was ineffective for labor pain relief but, when combined with intrathecal sufentanil, reduced the effective dose 50 of sufentanil by approximately 25%.⁴¹

Epidural administration (100-200 μ g) appears to avoid these clinically troublesome adverse effects, while still improving local anesthetic-induced analgesia.⁴²⁻⁴³ Combinations of epidural neostigmine with local anesthetics, opioids, or clonidine for labor analgesia displayed analgesic effectiveness, potentiating analgesic effect of opioids and clonidine.⁴⁴⁻⁴⁶ Different doses of epidural neostigmine do not affect the motor blockade. Higher doses of intrathecal neostigmine can cause mild sedation.^{38,47}

Two different meta-analyses evaluated the effectiveness and side effects of intrathecal neostigmine in the perioperative and peripartum settings.^{48,49} They concluded that adding intrathecal neostigmine to other spinal medications improves perioperative and peripartum analgesia marginally when compared with placebo. The incidence of abnormal fetal heart rate or Apgar scores was not different. However, the addition of neostigmine to other epidural medications is associated with significant side effects and the disadvantages outweigh usually the minor improvement in analgesia achieved. Nausea and vomiting were seen less frequently in epidural neostigmine studies compared to intrathecal studies, thought to be arising due to less neostigmine diffusion from dura and absence of cephalic distribution.⁵⁰ Neostigmine stimulates muscarinic receptors in the bronchial smooth muscles and can lead to bronchospasm. In intrathecal neostigmine studies, except at very high doses (eg, 750 μ g), no change has been detected in oxyhemoglobin saturation and in end-tidal carbon dioxide levels.⁵¹

Intrathecal neostigmine at a dose of 1 μ g/kg has been used in pediatric lower abdominal and urologic surgeries where it was found to increase analgesia.^{52,53} Adverse gastrointestinal effects have made neostigmine an unpopular choice for neuraxial adjuvant therapy. Unlike intrathecal neostigmine, epidural neostigmine is not associated with an increased risk of nausea and vomiting; however, doses greater than 100 μ g have been associated with sedation. It does not cause respiratory depression or pruritus either alone or in combination with neuraxial opioids.

Ketamine

Anesthetic and subanesthetic doses of ketamine have analgesic properties as a result of noncompetitive antagonism of *N*-methyl-D-aspartate (NMDA) receptors. With prolonged, repetitive nociceptive stimulation NMDA receptors are activated, releasing excitatory neurotransmitters glutamate, aspartate, and neurokinin.⁵⁴ Its primary analgesic effect is mediated by antagonizing NMDA receptors located on secondary afferent

neurons in the dorsal horn of the spinal cord. These neurotransmitters are associated with many activities including central sensitization, windup, and the generation of plasticity of various systems such as memory, vision, motor function, and spinal sensory transmission.

There is little clinical use of intrathecal ketamine due to the potential risk of neurotoxicity in preservative-free form that caused spinal pathology in dogs⁵⁵ and from its preservative benzalkonium chloride.⁵⁶⁻⁵⁹ Spinal myopathy has been reported in a terminally ill cancer patient after continuous infusion intrathecal ketamine at a rate of 5 mg per day for a duration of 3 weeks of preservative-free ketamine.⁶⁰ Reported side effects of epidural ketamine include sedation, headache, and transient burning back pain during injection with doses greater than 0.5 mg/kg. The burning back pain is concerning for neurologic damage.

However, efficacy has been shown in several clinical trials that were completed before the toxicology was fully evaluated and known to be problematic. Naguib et al⁶¹ studied epidural doses of 10 and 30 mg of ketamine and found that 30-mg dose produced excellent postoperative pain relief for a longer duration. A low dose of ketamine at 4, 6, and 8 mg epidurally was found to be ineffective for postoperative analgesia.⁶²⁻⁶³ Caudally administered ketamine 0.5 mg/kg along with 0.175% levobupivacaine 1 mL/kg has been used successfully without adverse effects in children for lower abdominal and urologic surgeries.⁶⁴ Epidural infusion of 0.25 mg/kg per hour of S(+)-ketamine during thoracic surgery provides better postoperative analgesia than epidural 0.25% ropivacaine (Figure 8.2).⁶⁵ Both epidural infusions started before skin incision and were run at 6 mL per hour for the duration of surgical procedure.

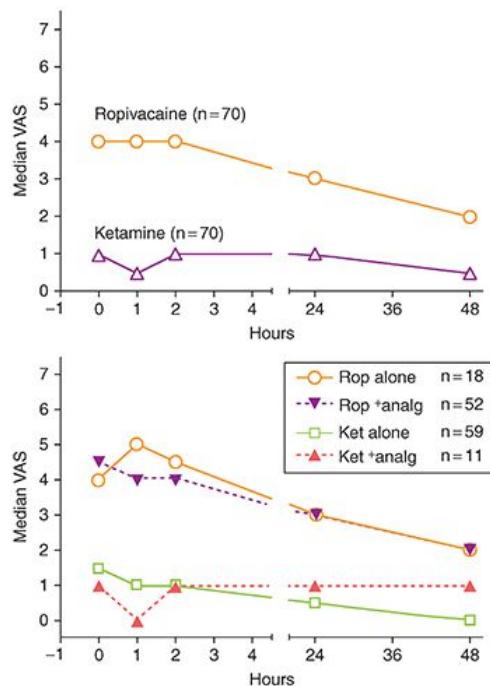


FIGURE 8.2 Postoperative median time courses of visual analog scale (VAS) scores in the ketamine (Ket) and ropivacaine (Rop) groups (upper panel) and in relation to analgesic consumption in the two groups (lower panel). Open symbols refer to no analgesics required; closed symbols refer to analgesics added. *Reprinted with permission from Feltracco P, Barbieri S, Rizzi S, et al. Brief report: perioperative analgesic efficacy and plasma concentrations of S+ -ketamine in continuous epidural infusion during thoracic surgery. Anesth Analg. 2013;116(6):1371-1375. Copyright © 2013 International Anesthesia Research Society.*

Combination of epidural ketamine with local anesthetic and/or opioid infusions results in improved analgesia, without significantly increasing adverse effects.^{11,66,67} The bupivacaine-ketamine mixture provided better analgesia than the bupivacaine solution alone.⁶⁶ Side effects such as motor weakness or urinary

retention were not observed in the ketamine group.⁶⁶ Adding small-dose ketamine to a multimodal epidural analgesia regimen provides better postoperative analgesia and reduces morphine consumption in thoracic, upper abdominal surgery, and lower abdominal surgeries.⁶⁵ Ketamine acts synergistically with opioids, dopaminergic, serotonergic, and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors to produce dissociation between the thalamocortical and limbic systems. α -Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid is a non-NMDA-type ionotropic glutamate receptor that mediates fast synaptic transmission in the CNS. Ketamine has shown efficacy in the management of neuropathic pain. In high doses, it may have additional minor analgesic effects by modulating descending inhibitory pathways through inhibition of reuptake of neurotransmitters.

No clinical trials have reported respiratory depression, hallucinations, cardiovascular instability, bladder dysfunction, or neurologic deficit with epidural doses up to 1 mg/kg. There is no increased incidence of nausea, vomiting, or pruritus when combined with neuraxial opioids. Intrathecal ketamine has been shown to decrease morphine requirements in patients with terminal cancer and is useful in opioid-tolerant patients. Intrathecal ketamine with bupivacaine had superior postoperative analgesic effect and prolonged the time to first request of rescue analgesia after major abdominal cancer surgery. When combined with dexmedetomidine and bupivacaine, it also reduced the total consumption of patient-controlled analgesia morphine but increased the incidence of postoperative sedation.⁶⁸ A randomized study comparing intrathecal morphine and ketamine added to bupivacaine concluded that adding 0.1 mg/kg of intrathecal ketamine to 0.3 mg of morphine in patients undergoing major abdominal surgery reduced the total consumption of morphine postoperatively in comparison with either drug alone. Ketamine has been administered intrathecally to 16 patients with war injuries of the lower limbs in varying doses from 5 to 50 mg in a volume of 3 mL of 5% dextrose.⁶⁹ It resulted in a distinct sensory level that was obtained in all patients and satisfactory surgical analgesia. Central effects (drowsiness, dizziness, and nystagmus) occurred in 9 patients, but they remained conscious throughout; 1 patient experienced no central effects, and 1 patient developed dissociative anesthesia. Ketamine alone did not produce motor block, but addition of adrenaline resulted in complete motor block and may have intensified sensory blockade.⁶⁹

Tramadol

Tramadol is an analgesic combining mainly μ -opioid and monoaminergic activity through the inhibition of the neuronal uptake of serotonin and NE.⁷⁰ Animal studies have confirmed the analgesic effect of intrathecally administered tramadol.

The results of intrathecal administration of tramadol to patients showed contradicting results.⁷¹⁻⁷⁴ Tramadol 1 to 2 mg/kg has also administered caudally in children for postoperative analgesia.⁷⁵

Epidural administration of tramadol has been studied in humans with mixed effects.⁷⁶⁻⁸¹

Droperidol

Epidural droperidol is effective for reducing pruritus and postoperative nausea and vomiting.⁸² Long-term intrathecal droperidol is used as an excellent antiemetic in nonmalignant pain.⁸³ It has been suggested that droperidol acts as a dopaminergic antagonist directly at the brainstem chemoreceptor trigger zone, the floor of the fourth ventricle, and other center locations are involved with antiemetic action. Although no side effects were observed, it is important to recognize the lack of laboratory data documenting the safety of neuraxial droperidol (including the potential for neurotoxicity).⁸⁴ In addition, there are many drugs that can be given systemically with a good safety record raising the question of the need for intrathecal delivery of an untested drug.

Conopeptides

Ziconotide

Ziconotide is a synthetic 25-amino acid, polybasic peptide with three disulfide bridges and is a derivative of an omega conotoxin founded in the venom of a *Conus magus* snail. Ziconotide acts as a selective blocker of

neuronal *N*-type voltage-sensitive calcium channels within the dorsal horn in the presynaptic terminals, inhibiting nerve transmission. In animal and healthy human studies, ziconotide directly inhibits central and peripheral NE release and functions as a sympatholytic, thus resulting in decrease in mean and diastolic pressure, mostly profound when administered intravenously and normally negligible when dosed intrathecally.

It is highly polar and water-soluble, hypobaric at clinically useful concentration, and has a relatively large molecular weight. It has narrow therapeutic window, so initial infusion rates should be limited to 0.1 µg per hour with stepwise increase of this rate over time; CNS adverse effects are to be expected.⁸⁵⁻⁸⁷ Ziconotide is the only on-label, FDA-approved, nonopioid intrathecally administered medication to treat neuropathic pain.

It produced spinal antinociception in animal models of acute and persistent pain,⁸⁸ and subsequent reports described its intrathecal administration to relieve severe neuropathic pain.⁸⁹⁻⁹² Intrathecal ziconotide is effective in reducing severe chronic noncancer pain, cancer-related pain, or AIDS-related pain that is refractory to other analgesic regimens.¹⁰

Unfortunately, side effects occurred in the majority of patients (92.9%) studied in a randomized, placebo-controlled study of intrathecal ziconotide in adults with severe chronic pain.⁹³ Significant adverse events reported in the ziconotide group were dizziness, confusion, ataxia, abnormal gait, and memory impairment. Suicidality was increased with ziconotide as compared to placebo. Most of the side effects are self-limiting with cessation of therapy.

Other Investigational Conopeptides

CGX-1160

Conopeptide contulakin-G (CGX-1160) is a conopeptide that produces analgesia by activation of neuropeptidergic receptor type 1. The drug has undergone proper toxicologic studies and has been successful in early clinical trials of patients with neuropathic pain related to spinal cord injury.^{94,95} Neuropeptidergic receptor agonists in general have been implicated in enhanced proliferation in some types of cancer leading along with financial matters to a pause in clinical development.

Another conopeptide that inactivates the $\alpha 9\alpha 10$ neuronal nicotinic receptor has been modified to create RgIA4 that is specific for both rodent and human receptors. This compound was found in animal studies to prevent chemotherapy induced neuropathy. Analgesic effects lasted for at least 3 weeks suggesting that the analgesia may be due to improvement in pathology.^{96,97} This compound is in early clinical development.

Octreotide

Octreotide is a synthetic octapeptide somatostatin derivative of human growth hormone. Octreotide administered spinally causes analgesia.^{98,99} Several clinical trials showed promise. Intrathecal octreotide administered to cancer patients for 5 years reduced pain without any adverse effects.¹⁰⁰ However, octreotide and its analogues have produced severe neurotoxicity in animals leading to a cessation of clinical study except in the setting of palliative care with experimental consent.

Baclofen

γ -Aminobutyric acid (GABA) acts as an inhibitory neurotransmitter in the CNS. Baclofen is an agonist of the GABA-B receptor. Baclofen suppresses neuronal transmission in the cerebral cortex, basal ganglia, thalamus, cerebellum, and spinal cord. The analgesic effects of baclofen are mediated postsynaptically via the activating the G protein-linked GABA-B receptors in laminae II and III that result in increased potassium conductance and membrane hyperpolarization. Baclofen also acts presynaptically to inhibit Ca^{+2} conductance, and, therefore, the release of glutamate and substance P, and postsynaptically to produce membrane hyperpolarization by increased potassium conductance through a G protein and second messenger system.¹⁰¹

Baclofen has low lipid solubility and low molecular weight that makes it an appropriate candidate for spinal action when delivered by the epidural route. However, continuous epidural baclofen infusion failed to prove to alter the pain-spasm cycle experienced by patients with cerebral palsy following orthopaedic

surgery.¹⁰² Intrathecal baclofen has demonstrated efficacy in chronic pain syndromes associated with multiple sclerosis and complex regional pain syndrome type I. For somatic pain, intrathecal baclofen has been used for the treatment of low back pain with root compression syndromes.¹⁰³ Intrathecal baclofen is specifically used for spasticity and dystonia due to various conditions such as cerebral palsy and spastic posttraumatic spinal cord injury. Recent interest has also focused on its use as an analgesic.¹⁰¹

A typical intrathecal dose of baclofen is 25 to 200 µg per day through a programmable intrathecal pump. Intrathecal administration is superior to systemic administration with regard to efficacy and adverse effects.¹⁰⁴ Baclofen has also been observed to relieve central pain syndromes in patients with spasticity,¹⁰⁵ although it is uncertain whether this is primarily an effect on musculoskeletal pain because of reduced spasticity or an effect on neuropathic spinal cord injury pain.¹⁰⁶ Some evidence suggests efficacy against nociceptive and neuropathic pain, particularly in combination with morphine and/or clonidine.

Baclofen has been investigated in the perioperative settings in a randomized, double-blinded study for total knee arthroplasty as an adjuvant with spinal bupivacaine as a 100-µg single dose. The results showed a statistically significant reduction in opioid use in the postanesthesia care unit, reduced pain scores in the 48 to 72 hours postoperatively, and a reduced likelihood and severity of pain at 3 months after total knee arthroplasty in patients who received intrathecal baclofen compared to those who received spinal bupivacaine and saline.¹⁰⁷ Common side effects of baclofen include sedation, drowsiness, headache, nausea, and weakness. More serious side effects such as rhabdomyolysis and multiple organ failure have also been reported.^{108,109}

Cyclooxygenase Inhibitors

Ketorolac

Constitutive expression of cyclooxygenase (COX)-1 and COX-2 in the spinal cord, upregulation of COX-1 and COX-2, and release and production of spinal prostaglandins occur after peripheral injury. Intrathecal injection of prostaglandins are found to cause hyperalgesia and allodynia.^{110,111} Ketorolac is a COX inhibitor drug. Thus, the intrathecal delivery of COX inhibitors theoretically would reduce pain and central sensitization. As such, targeted inhibition of spinal COX may be a viable strategy for treating pain. This has led many investigators to postulate and demonstrate that neuraxial administration of nonsteroidal antiinflammatory drugs produces analgesia following excitatory input into the spinal cord.^{112,113}

The pharmacokinetics of ketorolac in cerebrospinal fluid obtained from dog studies suggests fast elimination and delayed tissue uptake; therefore, continuous infusion of intrathecal ketorolac may be required. Animal data appear promising, and healthy volunteer studies did not identify adverse neurologic side effects. Understanding the relevance of these observations to pain in humans has been hampered by lack of regulatory approval for intrathecal injection of these products.^{114,115} Intrathecal injection of ketorolac was studied in humans in an open-label, dose-escalating safety study. Intrathecal ketorolac 0.25 to 2.0 mg was well tolerated, with the only adverse effect being a mild reduction in heart rate 15 to 60 minutes following injection.¹¹¹ Intrathecal ketorolac did not relieve chronic pain or extend anesthesia or analgesia from intrathecal bupivacaine administered at the beginning of surgery.¹¹¹ A single spinal dose of ketorolac did not reduce acute pain, acute opioid use, or pain incidence or severity 2 and 6 months after hip arthroplasty.¹¹⁶ These studies suggest that spinally produced prostaglandins may have a more limited role in pain and hypersensitivity in humans than predicted by animal studies, and intrathecal ketorolac may have limited analgesic effects in humans.

Magnesium Sulfate

Magnesium has analgesic properties, primarily related to the regulation of calcium influx into cells¹¹⁷ and antagonism of NMDA receptors in the CNS.^{118,119} In a rat, models showed that direct intrathecal administration of magnesium enhanced the antinociceptive effect of opioids for acute incisional pain¹²⁰ and suppresses nociceptive responses in neuropathic pain models.¹²¹ Several trials investigating the analgesic efficacy of perioperative intravenous magnesium have been published with conflicting results.^{122–124} The

earliest clinical trials investigating intrathecal and epidural magnesium reported an increase in the median duration of analgesia¹²⁵ and decrease in opioid consumption by 25%,¹²⁶ respectively.

Animal studies have reported histologic neurotoxicity with weight-adjusted doses similar to those used in most human clinical trials to date,¹²⁷⁻¹²⁹ whereas two case reports have described patients suffering from disorientation¹³⁰ and continuous periumbilical burning pain¹³¹ following the injection of magnesium into the neuroaxis. These findings limit the utility of further human studies.

Conclusion

Neuraxial drug administration via the intrathecal and epidural route remains an important treatment option for the provision of anesthesia as well as analgesia in acute, cancer, and chronic pain. Additional dose-effect studies would strengthen our understanding of the safety profile of drugs administered neuraxially before translation into routine clinical practice can be supported.

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Peripherally Acting Analgesics*

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An analgesic is any member of the group of drugs that are used to decrease pain sensation without loss of consciousness. An analgesic drug may act on the peripheral nervous system and/or central nervous system (CNS). Peripheral analgesics act at the sensory input level by blocking transmission of the impulse at a point peripheral to the brain/spinal cord. Their common denominator was thus believed to be their site of action within or proximal to the affected tissues, and hence, they were termed *peripheral analgesics*. Experimental and clinical studies support the possibility of plasticity within the dorsal root ganglion that is the way station between peripheral sensory afferents and spinal synaptic transmission. Peripheral administration of drugs can potentially optimize drug concentrations at the site of origin of pain, leading to lower systemic levels and fewer adverse systemic effects and drug interactions.

Recent efforts have been focused on peripherally selective compounds with limited ability to cross the blood–brain barrier. Nociceptive, inflammatory, and neuropathic pain all depends to some degree on the peripheral activation of primary sensory afferent neurons. A range of inflammatory mediators such as prostanoids, bradykinin, adenosine triphosphate, histamine, and serotonin can activate primary sensory afferent neurons. Inhibiting the actions of inflammatory mediators represents a strategy for the development of analgesics. Peripheral nerve endings also express a variety of inhibitory receptors including opioid, α -adrenergic, cholinergic, transient receptor potential cation channel subfamily V member 1, adenosine, and cannabinoid receptor, and ligands for these receptors represent viable targets for drug development. Transmission of a pain signal from the periphery to the CNS is complex. Tissue damage results in peripheral release of endogenous chemicals that can directly activate nociceptive afferent fibers, sensitize nociceptors, and/or cause increased local extravasation and vasodilatation. Nociceptive afferents have their cell bodies in the dorsal root ganglion and synapse with second-order neurons in the dorsal horn (for more details, see [Chapter 6](#)).

Nonsteroidal Antiinflammatory Drugs

Nonsteroidal antiinflammatory drugs (NSAIDs) are among the most often prescribed drugs in the world and have both central and peripheral effects that are principally due to blockade of the prostaglandin production. The NSAIDs have been shown to increase patient satisfaction and decrease opioid requirements.¹ This diverse class of drugs includes aspirin and other selective or nonselective cyclooxygenase (COX) inhibitors with common analgesic, antiinflammatory, and antipyretic properties.² The COX pathway is shown in [Figure 9.1](#). The NSAIDs inhibit the biosynthesis of prostaglandins by preventing the substrate arachidonic acid from binding to the COX enzyme active site.

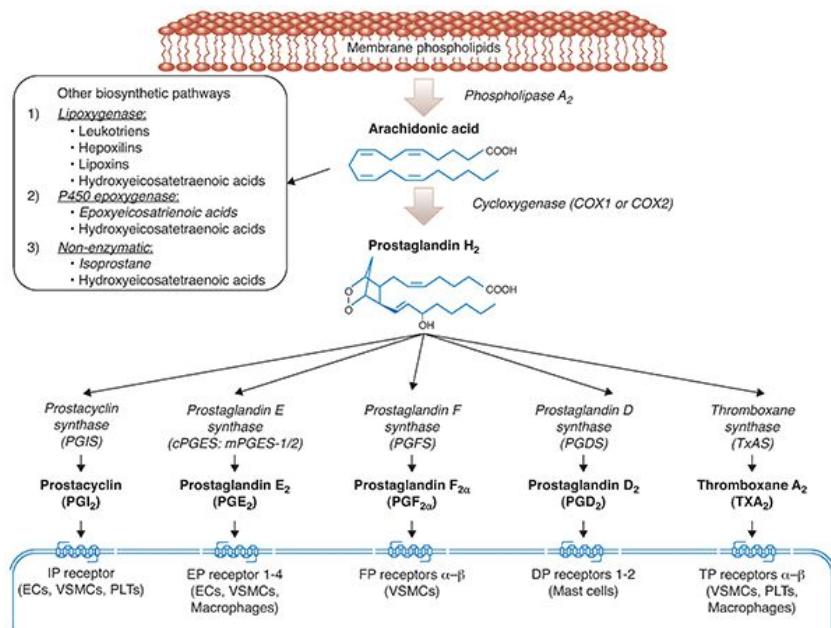


FIGURE 9.1 The cyclooxygenases pathway. Abbreviations: ECs, endothelial cells; EP, PGE₂ receptor; DP, PGD₂ receptor; FP, PGF_{2α} receptor; IP, prostacyclin receptor; PLTs, platelets; TP, thromboxane receptor; VSMCs, vascular smooth muscle cells.

The NSAIDs can be classified according to numerous characteristics, including COX selectivity and chemical and pharmacologic properties. The COX enzyme exist in two isoforms—cyclooxygenase 1 (COX-1) and cyclooxygenase 2 (COX-2) isoenzymes.² The COX-1 is constitutively expressed and catalyzes the production of prostaglandins that are involved in numerous physiologic functions, including maintenance of normal renal function in the kidneys, mucosal protection in the gastrointestinal tract, and proaggregatory thromboxane A2 in the platelets. The COX-2 expression can be induced by inflammatory mediators in many tissues and have a role in the mediation of pain, inflammation, and fever. There has been speculation on the existence of a third isoform, cyclooxygenase 3 (COX-3), which would explain the mechanism of action of acetaminophen, a poor inhibitor of COX-1 and COX-2. However, such an isoform has not been identified in humans. Evidence indicates that, in addition to peripheral blockade of prostaglandin synthesis, central inhibition of COX-2 may play an important role in modulating nociception.

No NSAIDs are completely COX-2 selective. The ratio for inhibition of COX-2/COX-1 is shown in [Figure 9.2](#). Two of the most COX-2-selective drugs are no longer clinically available due to an excess of cardiovascular events as described under “Cardiovascular Side Effects” discussed in the following text. Currently, celecoxib is the only partially COX-2-selective inhibitor available for clinical use. However, as shown in [Figure 9.2](#), diclofenac is only slightly less COX-2 selective than celecoxib. Ketorolac is the most COX-1-selective clinically used NSAID.

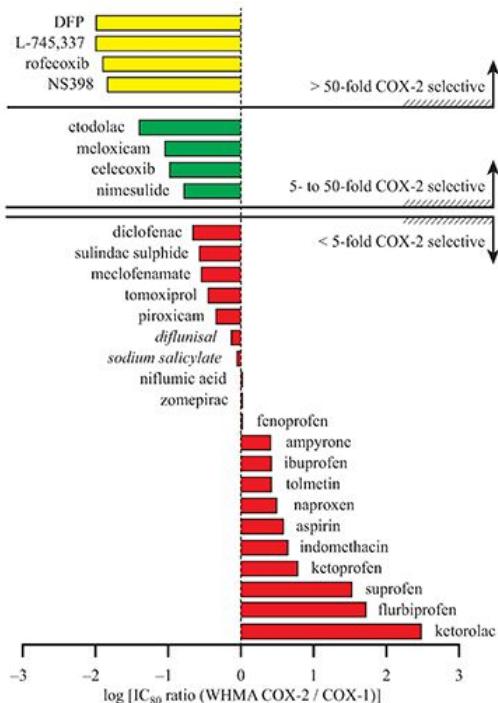


FIGURE 9.2 Relative selectivity of nonsteroidal antiinflammatory drugs for cyclooxygenase (COX) enzymes. Determinable $\log [IC_{80} \text{ ratio (WHMA-COX-2 / COX-1)}]$. The “0 line” indicates equipotency, that is, an IC_{80} ratio of 1. Italics indicate compounds with very low potency.

The COX-2-selective drugs may be a safer alternative to nonselective NSAIDs in the perioperative settings. Although analgesic activity is similar, NSAID use has been limited in the perioperative setting due to concerns about platelet dysfunction and gastrointestinal toxicity. The potential benefits of coxibs include improved quality of analgesia, reduced incidence of gastrointestinal side effects versus conventional NSAIDs, and no platelet inhibition.

Less Selective Nonsteroidal Antiinflammatory Drugs

The NSAIDs belong to a number of chemical families including acetic acids, oxicams, propionic acids, salicylates, fenamates, furanones, and coxibs (**Table 9.1**). All NSAIDs are weakly acidic chemical compounds and share similarities in pharmacokinetic properties.³ The volume of distribution of NSAIDs is low, ranging from 0.1 to 0.3 L/kg, suggesting minimal tissue binding. The plasma half-life of NSAIDs ranges from 0.25 to >70 hours, indicating wide differences in clearance rates. Hepatic or renal disease can alter NSAID protein binding and metabolism.⁴ In healthy, normovolemic patients treated with appropriate NSAIDs at clinically appropriate doses, hepatic and renal dysfunction is normally not problematic.

TABLE 9.1

Characteristics of commonly prescribed nonsteroidal antiinflammatory drugs (NSAIDs)

Generic name (Trade name)	Dose ^a		Pharmacokinetics	
	Available dosages (mg)	Common dosing intervals	Drug metabolism	Elimination half-life (h)
Nonselective NSAIDs				
Acetic acid group				
Diclofenac DR (Voltaren)	25	BID-TID QD-BID	Oxidation	1-2

	50			
Diclofenac XR (<i>Voltaren XR</i>)	75 100			
Etodolac (<i>Lodine</i>)	200 300	BID-TID QD	Oxidation, conjugation	7
Etodolac XL (<i>Lodine XL</i>)	400 500 400 500 600			
Ketorolac IM, IV injection (<i>generic</i>)	30	QD-QID	Conjugation	2.5-8.5
Indomethacin (<i>Indocin</i>)	25 50	BID-TID QD-BID	Oxidation, conjugation	4.5-6
Indomethacin SR (<i>Indocin SR</i>)	75			
Nabumetone (<i>Relafen</i>)	500 750	QD-BID	Oxidation	22-30
Sulindac (<i>Clinoril</i>)	150 200	BID	Oxidation, reduction	16
Tolmetin (<i>Tolectin</i>)	400 600	TID	Conjugation	5
Oxicam group				
Meloxicam (<i>Mobic</i>)	7.5 15	QD	Oxidation	13-20
Piroxicam (<i>Feldene</i>)	10 20	QD	Oxidation	30-86
Propionic acid group				
Fenoprofen (<i>Nalfon</i>)	200 300	TID-QID	Glucuronidation	3
Flurbiprofen (<i>Ocufen</i>)	50 100	BID-QID	Oxidation	3-6
Ibuprofen (<i>Motrin</i>)	400 600 800	TID-QID	Oxidation	2-2.5
Ketoprofen	50 75	TID-QID QD	Conjugation	2-4 3-7
Ketoprofen CR	100 150 200			

Naproxen (<i>Naprosyn</i>) (<i>Naprelan</i>)	250 375 500 375 500	BID QD	Conjugation, oxidation	12-15
Oxaprozin (<i>Daypro</i>)	600	QD-BID	Oxidation, conjugation	50-60
Salicylate				
Aspirin (<i>Ecotrin</i> , <i>Ascriptin</i>)	81 325	QD BID-QID	Hydrolysis, conjugation, glucuronidation	0.25-0.5
Choline magnesium				
Trisalicylate (<i>Trilisate</i>)	750 1000		Conjugation	2-12
Cyclooxygenase 2 agents				
Coxib group				
Celecoxib (<i>Celebrex</i>)	100 200	QD-BID	Conjugation	11-16

Abbreviations: BID, twice a day; IM, intramuscular; IV, intravascular; QD, everyday; TID, three times a day.

^aA dosage range exists for each NSAID that must be individualized depending on patient characteristics and disease mechanism.

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The NSAIDs generally have complete, rapid oral bioavailability. After absorption, NSAIDs are more than 90% bound to albumin, which is critical for its volume of distribution and apparent potency.

Hypoalbuminemia (eg, due to alcoholic liver disease) and displacement by other drugs that are albumin bound can result in greater unbound NSAID and increased risk for toxicity.⁴ The liver metabolizes most NSAIDs, with subsequent excretion into urine or bile. Enterohepatic recirculation occurs when a significant amount of an NSAID or its conjugated metabolites are excreted into the bile and then reabsorbed in the distal intestine. Hepatic NSAIDs elimination is dependent on the free fraction of NSAIDs within the plasma and the intrinsic enzyme activities in the liver. The NSAIDs are primarily eliminated by renal and biliary excretion. Moderate to severe liver disease impairs NSAIDs metabolism, increasing the potential for NSAIDs toxicity.

Side Effects of Nonsteroidal Antiinflammatory Drugs

Platelet Function

Platelet aggregation and thus the ability to clot is primarily induced through stimulating thromboxane production following activation of platelet COX-1. There are no COX-2 enzyme platelets. The NSAIDs and aspirin inhibit the activity of COX-1, but the COX-2-specific inhibitors (or COX-1 sparing drugs) have no effect on platelet aggregation.⁵

Gastrointestinal Side Effects

The NSAIDs are associated with a spectrum of upper gastrointestinal complications, ranging from endoscopic ulcers in 10% to 30% of patients, to serious ulcer complications in 1% to 2% of patients.^{6,7} Lower gastrointestinal tract complications are less well characterized.^{8,9} Risk factors for NSAID-associated gastrointestinal complications include high NSAID dose; older age; *Helicobacter pylori* infection; a history of ulcer; and concomitant use of low-dose aspirin, anticoagulants, or corticosteroids.^{10,11} Therefore, it is generally recommended that patients with gastrointestinal risk factors should be treated with COX-2-

selective agents or nonselective NSAIDs with gastroprotective cotherapy.^{12,13} The NSAIDs should be used cautiously in colorectal surgery because there is some association with increase the risk of anastomotic leak.¹

Cardiovascular Side Effects

The NSAIDs are associated with an increased risk of cardiovascular adverse events such as myocardial infarction, heart failure, and hypertension. A COX inhibition is likely to disturb the balance between COX-2-mediated production of proaggregatory thromboxane in platelets and antiaggregatory prostaglandin I₂ in endothelial cells. The COX selectivity alone is not sufficient to define the risk of NSAID-associated cardiovascular complications. Based on two studies, the Vioxx Gastrointestinal Outcomes Research study¹⁴ and the Adenomatous Polyp Prevention on Vioxx study,¹⁵ rofecoxib was withdrawn from the market in 2004. Valdecoxib was subsequently withdrawn in 2005 due to a fourfold increase in the incidence of myocardial infarction.

The cardiovascular safety of nonselective NSAIDs has been under investigation. A meta-analysis of randomized trials found that high-dose ibuprofen and high-dose diclofenac were associated with a moderately increased risk of vascular events compared with placebo, similar to that observed with COX-2-selective agents, but the risks associated with naproxen, although they cannot be completely excluded, were substantially lower.¹⁶

Studies are lacking on the long-term effects of nonselective NSAIDs on gastrointestinal and cardiovascular systems, which limit our understanding of the true benefits and risks of NSAIDs. To reduce the cardiovascular risk, the American Heart Association recommends that all NSAIDs should be used at their lowest effective dose. A recent meta-analysis confirms that vascular and upper gastrointestinal effects of NSAIDs that diclofenac and ibuprofen raise risk of major vascular events as much as celecoxib. Naproxen has no effect on vascular outcomes but still increases upper gastrointestinal complications.¹⁷ There is no apparent relationship to COX enzyme selectivity.

Renal Side Effects

The COX-1 is constitutively expressed in the kidney, and COX-2 is induced in response to injury and inflammation.¹⁸ The production of prostaglandins and thromboxane are regulated by the COX enzymes in conjunction with intravascular volume. The effects of the NSAIDs on renal function include changes in the excretion of sodium, changes in tubular function, the potential for interstitial nephritis, and reversible renal failure due to alterations in filtration rate and renal plasma flow. The COX-1 controls hemodynamics and glomerular filtration rate, and COX-2 affects salt and water balance. As such, drugs such as diuretics and angiotensin blockers put patients at risk for renal dysfunction in response to NSAIDS. Reduced renal function prolongs NSAID half-life, and the dose should be lowered proportionally in patients with impaired kidney function.^{3,4} Prostaglandins and prostacyclins are important for maintenance of intrarenal blood flow and tubular transport. All NSAIDs, except nonacetylated salicylates, have the potential to induce reversible impairment of glomerular filtration rate; this effect occurs more frequently in patients with congestive heart failure; established renal disease with altered intrarenal plasma flow including diabetes, hypertension, or atherosclerosis; and with induced hypovolemia, salt depletion, or significant hypoalbuminemia.^{19,20}

Liver Side Effects

The use of aspirin was associated with reduced risk of developing hepatocellular carcinoma and of death due to chronic liver disease, whereas nonaspirin NSAID use was only associated with reduced risk of death due to chronic liver disease.²¹ Elevations in hepatic transaminase levels and liver failure have been reported.²²

Pulmonary Side Effects

Many adverse reactions attributed to NSAIDs are due to inhibition of prostaglandin synthesis in local tissues. For example, patients with allergic rhinitis, nasal polyposis, and/or a history of asthma, in whom all NSAIDs effectively inhibit prostaglandin synthase, are at increased risk for anaphylaxis.²³ The use of selective COX-2 inhibitors as an alternative to aspirin and other NSAIDs has been suggested for patients with aspirin-

exacerbated respiratory disease. The highly selective COX-2 inhibitor etoricoxib has been shown to be tolerated in most but not all patients tested.²⁴ An oral provocation test is therefore recommended before prescribing etoricoxib for patients with aspirin-exacerbated respiratory disease.²⁴ Etoricoxib is not currently available in the United States.

Hypersensitivity Reactions

Hypersensitivity reactions to NSAIDs occur rarely, and they are more common in individuals with nasal polyps or asthma. Allergic reactions include bronchoconstriction, rhinitis, and urticaria. Recent data suggest a role of altered COX-2 regulation associated with the aspirin-intolerant asthma/rhinitis syndrome.²³ Because of the potential for cross-reactivity, avoidance of all NSAIDs is recommended after severe reaction. In rare cases, NSAIDs have been implicated in causing aseptic meningitis and, in children, Reye syndrome.²⁵ The most common toxicities associated with NSAIDs are gastrointestinal, cardiovascular, and renal and are related primarily to COX inhibition and decreased synthesis of prostaglandins.

Idiosyncratic Adverse Effects

A typical nonspecific reaction includes skin rash and photosensitivity, tinnitus, hearing loss, and neutropenia. The effect of prostaglandin inhibition may result in premature closure of the ductus arteriosus. Prenatal aspirin use has been associated with smaller babies and neonatal bruising; however, it has been used for many years in the treatment of patients who require NSAIDs while pregnant.²⁶ It is not clear whether the indication for aspirin use such as history of preeclampsia and pregnancy loss is responsible for the smaller for gestational age infants or a direct effect of aspirin.

Drug-Drug Interactions With Nonsteroidal Antiinflammatory Drugs

Drug-drug interactions with NSAID therapy may result from pharmacodynamic or pharmacokinetic interactions. Nonselective NSAIDs affect other antiplatelet agents via additive inhibition of platelet aggregation. The result is an increased bleeding risk with the concomitant use of NSAIDs and other antiplatelet agents.^{25,27}

Significant drug-drug interactions have been documented with use of NSAIDs and lithium. The NSAIDs decrease lithium clearance and increase serum lithium concentrations by inhibiting renal prostaglandin production and altering intrarenal blood flow.^{25,27,28} Data are conflicting regarding the drug-drug interaction potential of angiotensin-converting enzyme inhibitors and NSAIDs.²⁹

As previously mentioned, NSAIDs are highly albumin bound and can be displaced by other drugs that strongly bind albumen. Concurrent administration of digoxin and NSAIDs can decrease renal clearance of digoxin, increase plasma drug concentration, and potentiate digoxin toxicity. The NSAIDs interact with anticonvulsant agents such as phenytoin and valproic acid by displacing the anticonvulsants from their protein-binding sites, which increases the free drug concentration. Combination use of corticosteroids and aspirin can increase renal clearance of salicylate and significantly decrease plasma salicylate concentrations.^{27,28}

The NSAIDs can be used in selected critically ill patients but should be used judiciously because of the potential for toxic adverse events. The lowest effective dose of the NSAID should be used for the shortest duration indicated. Appropriate clinical and laboratory surveillance and follow-up is necessary.

Acetaminophen

Acetaminophen (Tylenol, also known as paracetamol, *N*-acetyl-*p*-aminophenol, and nAPAP) is a popular antipyretic and analgesic found in many over-the-counter and prescription products. Acetaminophen is antipyretic and analgesic but has little, if any, antiinflammatory action. Acetaminophen is the leading cause of acute liver failure in the United States, and nearly half of acetaminophen-associated cases are due to unintentional overdose. With current U.S. Food and Drug Administration (FDA) regulation, it is hard to imagine that acetaminophen would be available without a prescription due to its toxicity.

Acetaminophen's mechanism of action is not known. It is complex and includes the effects of both peripheral and central antinociception processes.³⁰ Acetaminophen has a central analgesic effect that is mediated through activation of descending serotonergic pathways. Debate exists about its primary site of action, which may be inhibition of prostaglandin synthesis. In animal models, acetaminophen has been shown to inhibit COX-3. At the spinal cord level, it antagonizes neurotransmission by *N*-methyl-D-aspartate (NMDA), substance P, and nitric oxide pathways. Various metabolites of acetaminophen such as *N*-acylphenolamine and *N*-acetyl-*p*-benzoquinoneimine induce antinociception by modulating transient receptor potential vanilloid 1 (TRPV1) and transient receptor potential ankyrin 1 in the spinal cord.^{31,32} There is also evidence that acetaminophen metabolites appear to mediate analgesia through stimulation of cannabinoid type 1 receptors in the rostral ventromedial medulla.³³

Oral acetaminophen has excellent bioavailability. Acetaminophen is suitable for analgesic or antipyretic uses; it is the first-line analgesic in osteoarthritis and particularly valuable for patients in whom aspirin is contraindicated (eg, those with peptic ulcer, aspirin hypersensitivity, children with a febrile illness). The conventional oral dose of acetaminophen is 325 to 650 mg every 4 to 6 hours; total daily doses should not exceed 4,000 mg (2,000 mg per day for chronic alcoholics). In 2009, an FDA advisory panel recommended a lower maximum daily dose of acetaminophen of 2,600 mg and a decrease in the maximum single dose from 1,000 to 650 mg.

Preparations of intravenous (IV) acetaminophen are currently available for clinical use. Optimal analgesia for moderate to severe postoperative pain cannot be achieved using a single agent alone.³⁴ The IV acetaminophen provides around 4 hours of effective analgesia for about 37% of patients with acute postoperative pain.³⁵ With its inherent safety and demonstrated efficacy, IV acetaminophen can prove to be an asset in managing perioperative pain. Current evidence suggests that a combination of acetaminophen and an NSAID may offer superior analgesia compared with either drug alone.³⁶ Studies in animals suggest synergy.³⁷

Acetaminophen is well tolerated and has a low incidence of gastrointestinal side effects. However, acute overdose can cause severe hepatic damage, and the number of accidental or deliberate poisonings with acetaminophen continues to grow. Chronic use of <2 g per day is not typically associated with hepatic dysfunction, but overuse of acetaminophen-containing narcotic and over-the-counter combination products marketed in the United States has led to heightened awareness of the possibility of toxicity.

Acetylsalicylic Acid (Aspirin)

Aspirin is the oldest and most widely used medicinal compound known in the world. It is considered separately from the other NSAIDs due to its predominant use in the treatment of cardiovascular and cerebrovascular diseases. It is an irreversible inhibition of COX enzymes. Aspirin is found in hundreds of over-the-counter medicines worldwide and remains at the forefront of medicine, with newly discovered applications for the prevention and treatment of several life-threatening diseases. Aspirin is a derivative of salicylic acid. Aspirin and salicylate are rapidly metabolized in the plasma (eg, plasma esterases), erythrocyte, and liver to salicylate in vivo.³⁸ Despite its rapid metabolism, it has long-lasting effects due to the fact that the COX enzymes are inhibited until new protein is produced.

Aspirin has several different approved uses. Aspirin acts as a general analgesic by blocking the action of the COX enzymes and thus prevents the production of prostaglandins. Aspirin effectively treats headaches, back and muscle pain, and other general aches and pains. In addition, aspirin produces inhibition of COX and, thus, prostanoid synthesis³⁹ and also protein kinase.⁴⁰ However, these are not necessarily the most likely mechanisms.⁴¹

Overdose

The mechanism of NSAIDs toxicity in overdose is related to both their acidic nature and their inhibition of prostaglandin production. The severity typically depends on the dose ingested and the salicylate concentration that correlates with the degree of acid-base disturbance.^{29,42} Salicylate levels of 300 to 600 mg/L are associated with mild toxicity, 600 to 800 mg/L with moderate toxicity, and greater than 800 mg/L

with severe toxicity. For nonselective NSAIDs, plasma concentrations are not commonly measured because the half-life of many of these agents is relatively short.⁴²

Symptoms include nausea, vomiting, abdominal pain, tinnitus, hearing impairment, and CNS depression (**Table 9.2**). With higher dose aspirin ingestion, metabolic acidosis, renal failure, CNS changes (eg, agitation, confusion, coma), and hyperventilation with respiratory alkalosis due to stimulation of the respiratory center. The presence of acidemia permits more salicylic acid to cross the blood–brain barrier.⁴³ With other nonselective NSAID ingestions, symptoms are similar.^{42–44}

TABLE 9.2

Adverse effects of nonsteroidal antiinflammatory drugs

System	Adverse effects
Cardiovascular	Hypertension; can exacerbate or induce heart failure, thrombotic events, possible increased risk of thrombotic/cardiovascular events with long-term use (use with caution in patients with preexisting disease; more likely with COX-2 inhibitors)
Respiratory	Nasal polyps, rhinitis, dyspnea, bronchospasm, angioedema; may exacerbate asthma
Hepatic	Hepatitis
Gastrointestinal	Gastropathy (can be asymptomatic), gastric bleeding, esophageal disease, pancreatitis
Hematologic	Increased intraoperative bleeding due to platelet inhibition/dysfunction (coxibs do not affect platelet function), will potentiate anticoagulation effect
Dermatologic	Urticaria, erythema multiforme, rash
Genitourinal	Renal insufficiency (use with caution in patients with preexisting renal disease), sodium/fluid retention, papillary necrosis, interstitial nephritis
Central nervous system	Headache, aseptic meningitis, hearing disturbances
Skeletal	Potential to inhibit bone growth/healing/formation
Pharmacologic interactions	NSAIDs displace albumin-bound drugs and can potentiate their effects (eg, warfarin).

Abbreviations: COX-2, cyclooxygenase 2; NSAIDs, nonsteroidal antiinflammatory drugs.

Management should be directed at symptomatic support, prevention of further absorption, and correction of acid-base imbalance.^{42–43} There is no antidote for salicylate or NSAID poisoning. Appropriate hydration and activated charcoal should be considered within 1 hour after aspirin ingestion. Urine alkalinization increases salicylate elimination.⁴² In severe cases of aspirin overdose, hemodialysis is effective at removing salicylate and correcting acid-base imbalances and has been shown to reduce morbidity and mortality.⁴³

Steroids

Glucocorticoids have been used to reduce inflammation and tissue damage in a variety of conditions, including inflammatory bowel disease and rheumatoid arthritis. The antiinflammatory action likely results from decreased production of various inflammatory mediators that play a major role in amplifying and maintenance of pain perception. Another proposed mechanism is by inhibition of phospholipase A2 as well as changes in cell function induced by glucocorticoid receptor activation.

Glucocorticoids have the most powerful antiinflammatory characteristics of all steroids. Corticosteroids are a subgroup of compounds known as adrenocorticoids that are naturally secreted from the adrenal gland. The primary corticosteroid is hydrocortisone, which is the standard against which the pharmacologic properties of various synthetic corticosteroids are judged. Many synthetic agents that are more potent, have longer durations of action, have greater antiinflammatory activity, and generate fewer unwanted mineralocorticoid side effects than hydrocortisone have been developed. Mineralocorticoids are adrenal cortical steroid hormones that have a greater effect on water and electrolyte balance. The main endogenous hormone is aldosterone.

Different steroids vary with respect to their duration of action and relative corticosteroid and mineralocorticoid activity. Corticosteroids are divided into short-, intermediate-, and long-acting groups ([Table 9.3](#)). Short- and long-acting preparations cause less inhibition of the hypothalamic-pituitary-adrenal axis. Many of the unwanted side effects are related to the mineralocorticoid properties.

Nearly all routes of administration can be used for corticosteroids. Although associated with significant toxicity when administered in large doses for long periods, adverse effects with a single dose of dexamethasone are usually minor but may increase plasma glucose in diabetics.[45](#)

TABLE 9.3

Comparative pharmacology of endogenous and synthetic corticosteroids

	Antiinflammatory potency	Sodium-retaining potency	Equivalent dose (mg)	Elimination half-time (h)	Duration of action (h)	Route of administration
Cortisol	1	1	20	1.5-3.0	8-12	Oral, topical, IV, IM, IA
Cortisone	0.8	0.8	25	0.5	8-36	Oral, topical, IV, IM, IA
Prednisolone	4	0.8	5	2-4	12-36	Oral, topical, IV, IM, IA
Prednisone	4	0.8	5	2-4	12-36	Oral
Methylprednisolone	5	0.5	4	2-4	12-36	Oral, topical, IV, IM, IA, epidural
Betamethasone	25	0	0.75	5	36-54	Oral, topical, IV, IM, IA
Dexamethasone	25	0	0.75	3.5-5.0	36-54	Oral, topical, IV, IM, IA
Triamcinolone	5	0	4	3.5	12-36	Oral, topical, IV, IM, epidural
Fludrocortisone	10	250	2	—	24	Oral, topical, IV, IM
Aldosterone	0	3,000				

Abbreviations: IA, intraarticular; IM, intramuscular; IV, intravenous.

The use of corticosteroids for pain relief, although popular, has yet to gain wider acceptance because of concerns over side effects, such as adrenal suppression, osteonecrosis, impaired wound healing ([Table 9.4](#)), and concerns about efficacy. There is evidence supporting the use of corticosteroids in multimodal analgesia protocols to contribute to the postoperative recovery of the patient by minimizing opioid doses and therefore side effects. However, the optimal mode, dose, and timing of administration remain unclear.[46](#)

TABLE 9.4

Potential side effects associated with corticosteroid therapy

Dermatologic and soft tissue

Skin thinning and purpura

Cushingoid appearance

Alopecia

Acne

Hirsutism

Striae

Hypertrichosis

Eye

Posterior subcapsular cataract

Elevated intraocular pressure/glaucoma

Exophthalmos

Cardiovascular

Hypertension

Perturbations of serum lipoproteins

Premature atherosclerotic disease

Arrhythmias with pulse infusions

Gastrointestinal

Gastritis

Peptic ulcer disease

Pancreatitis
Steatohepatitis
Visceral perforation

Renal
Hypokalemia
Fluid volume shifts

Genitourinary and reproductive
Amenorrhea/infertility
Intrauterine growth retardation

Bone
Osteoporosis
Avascular necrosis

Muscle
Myopathy

Neuropsychiatric
Euphoria
Dysphoria/depression
Insomnia/akathisia
Psychosis
Pseudo tumor cerebri

Endocrine
Diabetes mellitus
Hypothalamic-pituitary-adrenal insufficiency

Infectious disease
Heightened risk of typical infections
Opportunistic infections
Herpes zoster

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In a meta-analysis,⁴⁷ patients treated with dexamethasone experienced less postoperative pain, required less postoperative opioids, had longer time to first analgesic dose, needed less rescue analgesia, and had shorter postanesthesia care unit stays. However, there was significant heterogeneity, and the differences between the groups were however small and may not be clinically relevant. Perioperative dose of dexamethasone had small but statistically significant analgesic benefits.⁴⁷ Investigators have begun to evaluate glucocorticoids as adjuvants for regional anesthesia. There is some evidence showed the analgesic effect of local spinal and systemic corticosteroids in combination with bupivacaine.⁴⁸ Dexamethasone have been found to prolong the block duration in animal and human studies, and adding methylprednisolone to local anesthetic increases the duration of axillary brachial block.⁴⁹

Dexamethasone also prolongs the analgesia from interscalene blocks using ropivacaine or bupivacaine, with the effect being stronger with ropivacaine; the combined effect of dexamethasone and either drug produced nearly 22 hours of analgesia. However, systemic glucocorticoids have also been shown to reduce postoperative pain. This raises the question whether the beneficial effects of adding glucocorticoid to a regional anesthetic is solely due to local effect or is mediated at least in part by systemic action.⁵⁰

Steroids are often administered to patients with arthritis and other chronic pain conditions locally (eg, intra-articularly) to limit the systemic side effect profiles. Pain relief from glucocorticoid treatment has been reported to last for up to 3 weeks in osteoarthritis and 2 months in rheumatoid arthritis.⁵¹

Epidural steroid injection has been used to treat back pain (mainly due to nerve root irritation) in patients with a wide variety of spine pathologies including radiculopathy, spinal stenosis, disk-space narrowing, annular tears, spondylosis, spondylolisthesis, vertebral fractures, and postlaminectomy syndrome.⁵¹

Systemic Local Anesthetics

Lidocaine produces analgesia by suppressing the activity of sodium channels in neurons that respond to noxious stimuli, thereby preventing nerve conduction and pain transmission. Voltage-gated sodium channels play a fundamental role in the control of neuronal excitability. Local anesthetics that block voltage-gated sodium channels have long been used to abolish pain temporarily by blocking nerve conduction.

Systemically administered local anesthetics, such as lidocaine, and orally administered mexiletine and tocainide are effective in a number of chronic pain conditions. Early studies described successful treatment of acute pain syndromes such as postoperative pain,⁵² burn pain,⁵³ and cancer pain.⁵⁴ Subsequent clinical reports have demonstrated the effectiveness in reducing pain associated with many chronic pain conditions.^{55,56} The exact mechanism of action of systemic local anesthetics in pain control is unknown. Evidence suggests that the effect may involve selective, dose-dependent blockade of pain fibers within the spinal cord or the dorsal root ganglia.⁵⁷ A Cochrane review assessed the effects of perioperative IV lidocaine infusion and concluded that it had a beneficial impact on pain scores in the early postoperative phase and on gastrointestinal recovery, postoperative nausea, and opioid consumption. However, the quality of evidence was limited due to inconsistency, imprecision, and quality of studies. Perioperative lidocaine infusion probably has no clinically relevant effect on pain scores later than 24 hours.⁵⁸ In contrast, when used for chronic neuropathic pain, there is evidence for long-term efficacy. At low concentrations, the analgesic effect is through sodium channel blockade. At increasing concentrations, there are off-target effects that are associated toxicity ([Figure 9.3](#)).⁵⁹

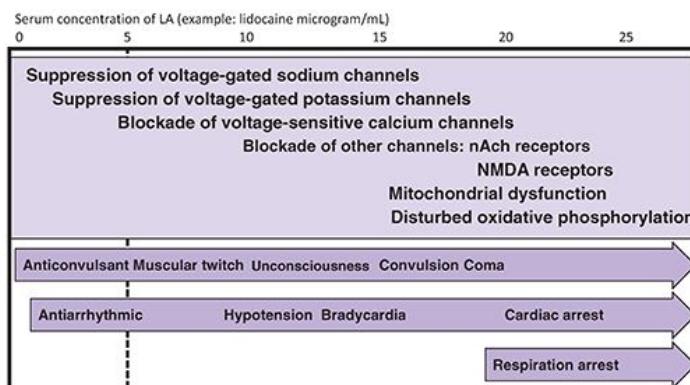


FIGURE 9.3 Systemic lidocaine concentration and toxicity. Intravenous lidocaine is kept between 1 and 5 µg/mL for the treatment of perioperative and chronic pain. Toxicity increases as specificity for voltage-gated sodium channels increases. nAch, nicotinic acetylcholine; NMDA, *N*-methyl-D-aspartate. *From Sekimoto K, Tobe M, Saito S. Local anesthetic toxicity: acute and chronic management. Acute Med Surg. 2017;4(2):152-160. <https://creativecommons.org/licenses/by/4.0/>.*

Orally administered lidocaine has poor bioavailability. The elimination half-life is 1.5 to 2 hours and can increase in the event of decreased liver blood flow (eg, congestive heart failure). Mexiletine has excellent oral bioavailability. The mean elimination half-life is 10 to 12 hours, which can increase to 25 hours with hepatic impairment. Only 10% of the drug is excreted unchanged by the kidney, and therefore, renal impairment has minimal effect on half-life.⁶⁰ A meta-analysis of studies of lidocaine and mexiletine used for neuropathic pain found that the drugs were superior to placebo, not different than other commonly used analgesics for this condition, and had no major adverse events when used within prescribed dosing and concentration guidelines.^{59,61}

At low doses, initial CNS symptoms include light-headedness, dizziness, tinnitus, vertigo, blurred vision, and altered taste. Seizures occur at higher doses. Cardiovascular side effects include hypotension, bradycardia, and cardiovascular collapse, which can lead to cardiac arrest.

Topical Application of 5% Lidocaine

The topical application of 5% lidocaine has been used in postherpetic neuralgia, and the topical application of 5% lidocaine (as a gel or patch) has been demonstrated to significantly relieve pain and reduce pain intensity with a fast onset (within 30 minutes) and lasting for the duration of drug application.⁶² Additionally, studies have also shown that lidocaine patches can provide pain relief in patients with other painful neuropathies.⁶³

Transdermal lidocaine has also been found to be effective after several different surgical procedures.^{64,65} The most common adverse events generally involve mild skin reactions. There has been no reported drug-drug interaction in clinical trials. Recent evidence suggests that extended application does not result in A β -mediated sensory loss at the application site, which is particularly important in patients who already have a degree of sensory loss due to their underlying condition. Heating a lidocaine patch can cause high systemic concentrations. Otherwise, the lidocaine patch provides a treatment option that carries a relatively low systemic adverse event and drug-drug interaction risk burden, even with continuous application of up to three patches per day. The efficacy of this approach alone can be a useful adjuvant for postoperative pain management.

Capsaicin

Capsaicin is a TRPV1 channel agonist.⁶⁶ A TRPV1 is a receptor that is activated in inflammatory conditions and is present on unmyelinated C fiber endings in the periphery.⁶⁷ The activation of the TRPV receptors releases high-intensity impulses and releases substance P and other inflammatory mediators, which results in the initial phase of burning. Continued release of substance P in the presence of capsaicin leads to the depletion of capsaicin and a subsequent decrease in C fiber activation.⁶⁸ Capsaicin is the major pungent ingredient of hot chili peppers and other botanicals. Capsaicin 0.025%, 0.075%, and 0.25% creams and/or transdermal patches are available over-the-counter for the temporary relief of pain from arthritis, myalgias, arthralgias, and neuralgias. The FDA has granted capsaicin orphan drug status in the treatment of postherpetic neuralgia, intermetatarsal neuroma, erythromelalgia, and human immunodeficiency virus-associated neuropathy. When used in the treatment of postherpetic neuralgia, a single transdermal application of a high-dose capsaicin patch (8%) provided a pain intensity decrease of $\geq 30\%$ for $> 35\%$ of treated patients in weeks 2 to 12.⁶⁹ Acute treatment with the high-dose capsaicin patch can be painful and requires pretreatment with topical or regional analgesia. The FDA approved the prescription-only capsaicin 8% patch for the management of neuropathic pain associated with postherpetic neuralgia. Topically applied capsaicin has moderate to poor efficacy in the treatment of chronic musculoskeletal or neuropathic pain.⁷⁰

Ketamine

There has been a renewed interest in the use of subanesthetic doses of ketamine as an adjunct to provide postoperative pain relief in opioid-dependent patients.⁷¹ The NMDA receptor antagonists have been used in perioperative pain management. At low subanesthetic doses, ketamine exerts NMDA blockade and modulates central sensitization than can be induced both by the incision and tissue damage and by long-term perioperative analgesics such as opioids. A Cochrane review that included 130 studies noted that IV ketamine probably reduced postoperative analgesic consumption and pain intensity.⁷²

There is a role of ketamine in preventing opioid-induced hyperalgesia in patients receiving high doses of opioid for their postoperative pain relief.⁷³ However, ketamine treatment can be limited due to psychotomimetic adverse effects. Other common adverse effects include dizziness, blurred vision, and nausea and vomiting that can be treated acutely or prophylactically.⁷⁴

Topical ketamine has been investigated. The NMDA and other glutamate receptors are present on sensory nerve endings and on cells adjacent to nerve endings. Inflammation and tissue damage result in elevated glutamate release from primary afferent nerve endings and keratinocytes. These findings suggest potential utility of topical application of NMDA receptor antagonists. Several controlled studies have compared topical ketamine with placebo. Ketamine 0.5% to 1.0% had no effect compared with placebo on neuropathic pain.⁷⁵ However, some controlled trial showed that topical ketamine with other drugs produced reduction in pain compared with placebo.⁷⁶ Currently, topical ketamine is only available as a compounded treatment.

Clonidine

Clonidine was developed as an antihypertensive drug in the 1960s that acts via nonspecific activation of α_1 - and α_2 -adrenergic receptors. In the intervening years, clonidine has been found to be effective for other indications including treating the symptoms of drug withdrawal. Clonidine has been used in the neuraxial and in combination with peripheral nerve blocks.⁷⁷ There is mixed data about how topical and systemic administration of clonidine could support the usefulness of low-dose IV administration.⁷⁸

Dexmedetomidine

Dexmedetomidine is a highly selective central α_2 agonist with little effect on α_1 -adrenergic receptors. Its sedative, proanesthetic, and proanalgesic effects at 0.5 to 2 $\mu\text{g}/\text{kg}$ given intravenously stem mainly from its ability to blunt the central sympathetic response. It minimizes opioid-induced muscle rigidity, lessens postoperative shivering, causes minimal respiratory depression, and has hemodynamic stabilizing effects. Dexmedetomidine, when used as an adjunct, can reduce postoperative morphine consumption in various surgical settings.^{79,80} A Cochrane database review showed that dexmedetomidine had some opioid-sparing effect but no clinically important differences in postoperative pain when compared with placebo.⁸¹ A recent meta-analysis evaluated the analgesic effect of intraarticular dexmedetomidine in knee arthroscopy and revealed that intraarticular dexmedetomidine significantly improved postoperative pain without any change in the incidence of nausea and vomiting, hypotension, bradycardia, or somnolence. More evidence is needed to confirm these findings.⁸²

Opioids

Since the detection of morphine in 1806 when morphine was extracted from opium, tested, and then marketed by the pharmacologist/pharmacist Friedrich Sertürner, it has been a mainstay of analgesic treatment. In addition to the central site of action, peripheral endogenous opioid analgesic systems have been extensively studied. The three classes of opioid receptors are widely distributed in peripheral as well as central neurons. Opioid receptors are synthesized in the dorsal root ganglia and transported centrally and peripherally to the nerve terminals.⁸³ They are also found in nonneuronal cells (neuroendocrine [pituitary, adrenals], ectodermal cells, and immune cells). The importance of the expression and activity of opioid receptors in microglia are increasingly found to be important to the transition to and the maintenance of chronic pain.⁸⁴

Efforts to develop peripherally restricted opioid analgesics (unable to cross the blood–brain barrier) that provide analgesia without central side effects are ongoing. Although peripheral opioid receptors expressed by the primary sensory neurons are functionally inactive under basal conditions, they are activated after surgery and trauma.⁸⁵ Several studies indicate that a large portion of the analgesic effects produced by systemically administered opioids can be mediated by peripheral opioid receptors.⁸⁶ Inflammation not only increases expression, transport, and accumulation of peripheral opioid receptors on peripheral terminals of sensory nerves but also triggers migration of opioid-containing immunocytes.⁸⁷ The peripheral effectiveness of opioids depends on the presence of inflammation, which triggers an enhanced expression of opioid receptors on primary afferents. Opioids were shown to have peripheral antinociceptive effects via modulation of inflammation.^{88,89} Interestingly, this recruitment of opioid-containing cells to inflamed tissue has been shown to be suppressed by the administration of centrally acting opioids.⁹⁰

Opioids injected locally into soft tissues or joints produce potent analgesic effects that are mediated by peripheral opioid receptors, occurring in the absence of central analgesic activity.⁹¹ Pain relief has been reported after knee arthroscopy on intra-articular injections of morphine⁹² and after submucosal injection of morphine in patients undergoing dental surgery.⁹³ There is some question about the complete peripheral restriction in these studies. The peripherally restricted μ -opioid agonist, loperamide, that is widely used for the treatment of diarrhea has only been implicated in animal models with antinociceptive activity except for the relief of cramping.⁹⁴ It may be that compounds that act on other peripheral opioid receptor subtypes could have more utility.⁹⁵ Opioid receptor activation plays a role in wound healing.⁹⁶ Peripherally acting opioids can reduce plasma extravasation, vasodilation, proinflammatory neuropeptides, immune mediators, and tissue

destruction. Local administration of opioid agonists at low concentrations may offer a promising therapeutic strategy.^{93,97}

There is strong evidence for a cardioprotective effect of both peripheral and central opioid receptors. There is some evidence that opioids may have infarct-sparing effects and ischemic preconditioning.⁹⁸ The endogenous opioid system is involved in the analgesic effect of the nonopioid analgesic celecoxib. There is evidence for both central⁹⁹ and peripheral¹⁰⁰ opioid receptor activation. In addition, there is evidence from animal models for antinociception from peripherally acting opioid agonists in models of inflammatory arthropathy and inflammatory bowel disease.^{101,102} Taken together, these findings underscore the potential utility of novel peripherally restricted opioids. In conclusion, peripherally acting analgesics have the benefit of avoiding central toxic side effects. We have provided examples of drugs that are given through local, regional, and systemic administration that have significant peripheral analgesic activity. In many cases, it is difficult to completely separate peripheral from central activity. The promise of peripherally restricted analgesics that can be used systemically as an opioid alternative is under active investigation.⁹⁵

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Local Anesthetics

Kamal Maheshwari • Mohamed A. Naguib[†]

Local anesthetics are used to provide analgesia and anesthesia for various surgical and nonsurgical procedures. Also, these drugs are used for acute and chronic pain management to reduce perioperative stress, to improve perioperative outcomes, and to treat dysrhythmias. Local anesthetics produce reversible conduction blockade of impulses along central and peripheral nerve pathways. With progressive increases in concentrations of local anesthetics, the transmission of autonomic, somatic sensory, and somatic motor impulses is interrupted, producing autonomic nervous system blockade, sensory anesthesia, and skeletal muscle paralysis in the area innervated by the affected nerve.

Koller introduced cocaine as the first local anesthetic in 1884, for use in ophthalmology. Halsted recognized the ability of injected cocaine to interrupt nerve impulse conduction, leading to the introduction of peripheral nerve block anesthesia and spinal anesthesia.¹ Cocaine (an ester of benzoic acid) is present in large amounts in the leaves of *Erythroxylum coca*, a plant growing in the Andes Mountains, where its cerebral-stimulating qualities are well known. Another unique feature of cocaine is its ability to produce localized vasoconstriction, making it useful to shrink the nasal mucosa in rhinolaryngologic procedures and nasotracheal intubation. The first synthetic local anesthetic was the ester derivative procaine, introduced by Einhorn in 1905. Lidocaine was synthesized as an amide local anesthetic by Lofgren in 1943. It produces more rapid, intense, and longer lasting conduction blockade than procaine. Unlike procaine, lidocaine is effective topically and is a highly efficacious cardiac antidysrhythmic drug. For these reasons, lidocaine is the standard to which all other anesthetics are compared.

Molecular Structure

Local anesthetics consist of a lipophilic and a hydrophilic portion separated by a connecting hydrocarbon chain (**Figure 10.1**). The hydrophilic group is usually a tertiary amine, such as diethylamine, whereas the lipophilic portion is usually an unsaturated aromatic ring, such as para-aminobenzoic acid. The lipophilic portion is essential for anesthetic activity, and therapeutically useful local anesthetics require a delicate balance between lipid solubility and water solubility. An ester (–CO–) or an amide (–NHC–) bond links the hydrocarbon chain to the lipophilic aromatic ring. The nature of this bond is the basis for classifying drugs that produce conduction blockade of nerve impulses as ester local anesthetics or amide local anesthetics (**Figure 10.2**). The important differences between ester and amide local anesthetics relate to the site of metabolism and the potential to produce allergic reactions. Local anesthetics are poorly soluble in water and therefore are marketed most often as water-soluble hydrochloride salts. These hydrochloride salt solutions are acidic (pH 6), contributing to the stability of the local anesthetic. An acidic pH is also important if epinephrine is present in the local anesthetic solution because this catecholamine is unstable at an alkaline pH. Sodium bisulfite, which is strongly acidic, may be added to commercially prepared local anesthetic-epinephrine solutions (pH 4) to prevent oxidative decomposition of epinephrine.

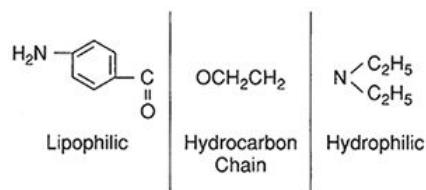


FIGURE 10.1 Local anesthetics consist of a lipophilic and hydrophilic portion separated by a connecting hydrocarbon chain.

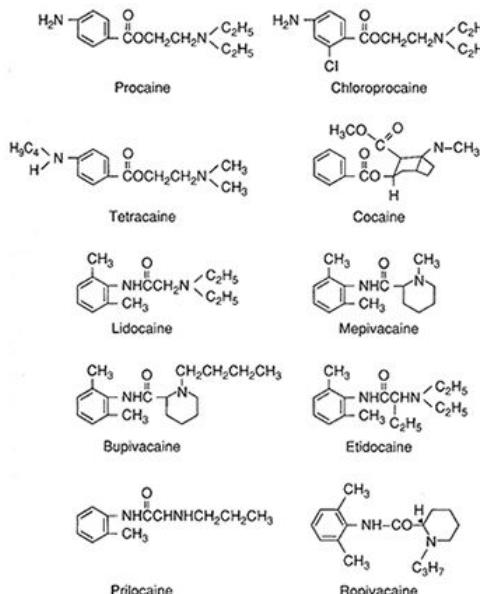


FIGURE 10.2 Ester and amide local anesthetics. Mepivacaine, bupivacaine, and ropivacaine are chiral drugs because the molecules possess an asymmetric carbon atom.

Structure-Activity Relationships

Modifying the chemical structure of a local anesthetic alters its pharmacologic effects. Lengthening the connecting hydrocarbon chain or increasing the number of carbon atoms on the tertiary amine or aromatic ring often results in a local anesthetic with a different lipid solubility, potency, rate of metabolism, and duration of action (**Table 10.1**). For example, substituting a butyl group for the amine group on the benzene ring of procaine results in tetracaine. Compared with procaine, tetracaine is more lipid soluble, is 10 times more potent, and has a longer duration of action corresponding to a 4- to 5-fold decrease in the rate of metabolism. Halogenation of procaine to chloroprocaine results in a 3- to 4-fold increase in the hydrolysis rate of chloroprocaine by plasma cholinesterase. This rapid hydrolysis rate of chloroprocaine limits the duration of action and systemic toxicity of this local anesthetic. Etidocaine resembles lidocaine, but substituting a propyl group for an ethyl group at the amine end and adding an ethyl group on the alpha carbon of the connecting hydrocarbon chain produces a 50-fold increase in lipid solubility and a 2- to 3-fold increase in the duration of action.

TABLE 10.1

Comparative pharmacology of local anesthetics

Classification	Potency	Onset	Duration after infiltration (minutes)	Maximum single dose for infiltration (mg)	Toxic plasma concentration ($\mu\text{g/mL}$)	pK binding (%)
Esters						
Procaine	1	Slow	45-60	500		8.9 6
Chloroprocaine	4	Rapid	30-45	600		8.7
Tetracaine	16	Slow	60-180	100 (topical)		8.5 76
Amides						
Lidocaine	1	Rapid	60-120	300	>5	7.9 70
Prilocaine	1	Slow	60-120	400	>5	7.9 55
Mepivacaine	1	Slow	90-180	300	>5	7.6 77

Bupivacaine	4	Slow	240-480	175	>3	8.1	95
Levobupivacaine	4	Slow	240-480	175		8.1	>97
Ropivacaine	4	Slow	240-480	200	>4	8.1	94
Classification	Fraction nonionized (%) at pH 7.4	Fraction nonionized (%) at pH 7.6	Lipid solubility	Volume of distribution (L)	Clearance (L per minute)	Elimination half-time (minutes)	
Esters							
Procaine	3	5	0.6	65		9	
Chlorprocaine	5	7		35		7	
Tetracaine	7	11	80				
Amides							
Lidocaine	25	33	2.9	91	0.95	96	
Prilocaine	24	33	0.9	191		96	
Mepivacaine	39	50	1	84	9.78	114	
Bupivacaine	17	24	28	73	0.47	210	
Levobupivacaine	17	24		55		156	
Ropivacaine	17			59	0.44	108	

Adapted from Denson DD. Physiology and pharmacology of local anesthetics. In: Sinatra RS, Hord AH, Ginsberg B, Preble LM, eds. *Acute Pain. Mechanisms and Management*. St Louis, MO: Mosby Year Book; 1992:124 and Burn AG, van der Meer AD, van Kleef JW, et al. Pharmacokinetics of the enantiomers of bupivacaine following intravenous administration of the racemate. *Br J Clin Pharmacol*. 1994;38:125-129.

Mepivacaine, bupivacaine, and ropivacaine are characterized as pipecoloxylidides (see [Figure 10.2](#)). Mepivacaine has a methyl group on the piperidine nitrogen atom (amine end) of the molecule. Addition of a butyl group to the piperidine nitrogen of mepivacaine results in bupivacaine, which is 35 times more lipid soluble and has a potency and duration of action 3 to 4 times that of mepivacaine. Ropivacaine structurally resembles bupivacaine and mepivacaine, with a propyl group on the piperidine nitrogen atom of the molecule. Despite the similar structure, ropivacaine causes less central nervous system (CNS) symptoms and is at least 25% less toxic than bupivacaine in regard to the dose tolerated,² highlighting even small difference in structure can lead to marked difference in pharmacokinetics and pharmacodynamics of local anesthetics.

Racemic Mixtures or Pure Isomers

The pipecoloxylidide local anesthetics (mepivacaine, bupivacaine, ropivacaine, levobupivacaine) are chiral drugs because their molecules possess an asymmetric carbon atom (see [Figure 10.2](#)). As such, these drugs may have a left- (S) or right- (R) handed configuration. Mepivacaine and bupivacaine are available for clinical use as racemic mixtures (50:50 mixture) of the enantiomers. The enantiomers of a chiral drug may vary in their pharmacokinetics, pharmacodynamics, and toxicity.³ These differences in pharmacologic activity reflect the fact that individual enantiomers bind to receptors or enzymes that are chiral amino acids with stereoselective properties. The S enantiomers of bupivacaine and mepivacaine appear to be less toxic than the commercially available racemic mixtures of these local anesthetics.⁴ In contrast to mepivacaine and bupivacaine, ropivacaine and levobupivacaine have been developed as a pure S enantiomers.⁵ These S enantiomers are considered to produce less neurotoxicity and cardiotoxicity than racemic mixtures or the R enantiomers of local anesthetics, perhaps reflecting decreased potency at sodium ion channel.⁶

Mechanism of Action

Local anesthetics bind to specific sites in voltage-gated sodium ion channels. They block sodium ion current, thereby reducing excitability of neuronal, cardiac, or CNS tissue.⁷ Local anesthetics prevent transmission of nerve impulses (conduction blockade) by inhibiting passage of sodium ions through ion-selective sodium channels in nerve membranes.⁸ The sodium channel itself is a specific receptor for local anesthetic molecules.

Failure of sodium ion channel permeability to increase slows the rate of depolarization such that threshold potential is not reached, and thus, an action potential is not propagated ([Figure 10.3](#)). Local anesthetics do not alter the resting transmembrane potential or threshold potential.

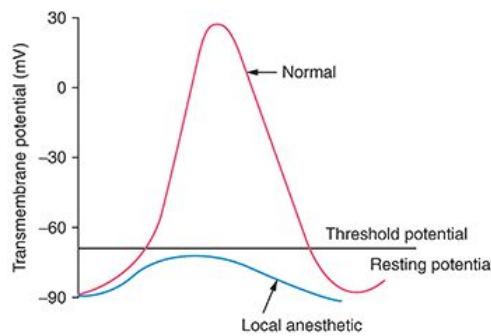


FIGURE 10.3 Local anesthetics slow the rate of depolarization of the nerve action potential such that the threshold potential is not reached. As a result, an action potential cannot be propagated in the presence of local anesthetic, and conduction blockade results.

Sodium Channels

The sodium channel is a dynamic transmembrane protein consisting of the large sodium-conducting pore (α subunit) and varying numbers of adjacent smaller β subunits. Nine distinct functional subtypes of voltage-gated sodium ion channels are recognized, corresponding to nine genes for their pore-forming α subunits. These have different tissue distributions in the adult and are differentially regulated at the cellular level by receptor-coupled cell signaling systems.⁹ Different isoforms of voltage-gated sodium ion channels, based on biophysical and pharmacologic studies, can provide distinct targets for interventions in various pain syndromes.^{10,11} The large polypeptide that forms the α subunit is further divided into four subunits (D I-D IV) ([Figure 10.4](#)). H is the α subunit that allows ion conduction and binds to local anesthetics. However, β subunits may modulate local anesthetic binding to the α subunit. Binding affinities of local anesthetics to the sodium ion channels are stereospecific and depend on the conformational state of the sodium channel.¹² Sodium channels exist in activated-open, inactivated-closed, and rested-closed states during various phases of the action potential.¹³ Voltage-gated sodium ion channels undergo fast and slow inactivation process, and this is critical for membrane excitability. The structural changes associated with inactivation process are poorly understood.¹⁴ In the resting nerve membrane, sodium channels are distributed in equilibrium between the rested-closed and inactivated-closed states. By selectively binding to sodium channels in inactivated-closed states, local anesthetic molecules stabilize these channels in this configuration and prevent their change to the rested-closed and activated-open states in response to nerve impulses. Sodium channels in the inactivated-closed state are not permeable to sodium, and thus, conduction of nerve impulses in the form of propagated action potentials cannot occur. It is speculated that local anesthetics bind to specific sites located on the inner portion of sodium channels (internal gate or H gate) as well as obstructing sodium channels near their external openings to maintain these channels in inactivated-closed states.⁸ This binding appears to be weak and to reflect a relatively poor fit of the local anesthetic molecule with the receptor. This is consistent with the broad variety of chemical structures that exhibit local anesthetic activity on sodium channels.¹²

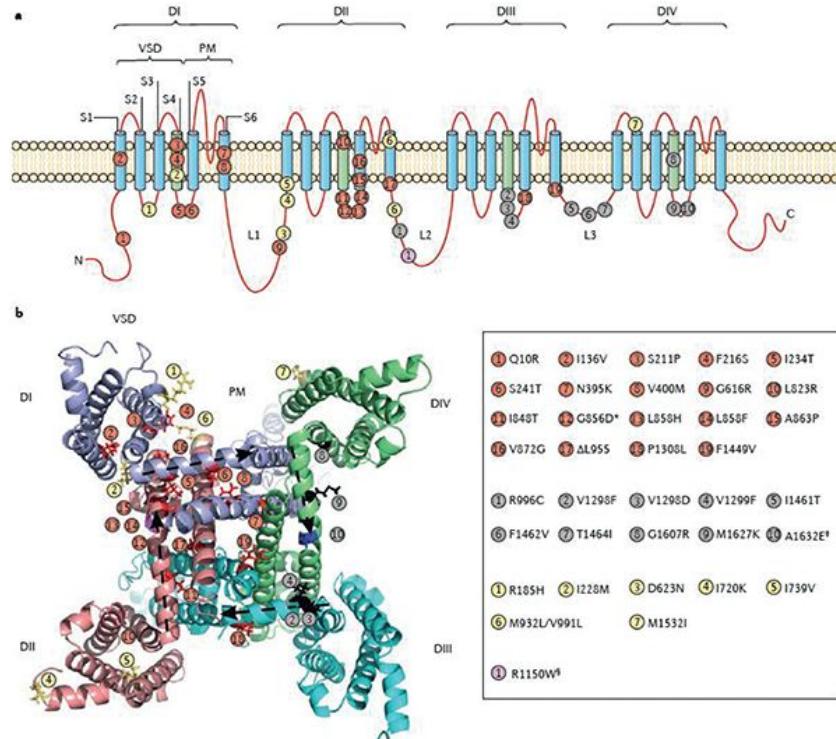


FIGURE 10.4 A, The sodium channel α subunit is a long polypeptide that folds into four homologous domains (DI-DIV), each of which consists of six transmembrane segments (S1-S6). The four domains are joined by three loops (L1-L3). Within each domain, S1-S4 comprise the voltage-sensing domain (VSD; S4, depicted in green, characteristically contains positively charged arginine and lysine residues), and S5-S6 and their extracellular linker comprise the pore module (PM). The linear schematic of the full-length channel shows the locations of amino acids affected by the gain-of-function *SCN9A* mutations that are linked to inherited erythromelalgia (red symbols), paroxysmal extreme pain disorder (gray symbols), and small-fiber neuropathy (yellow symbols). B, View of the folded $\text{Na}_V1.7$ from the intracellular side of the membrane based on the recently determined crystal structure of a bacterial sodium channel. The structure shows the central ion-conducting PM and four peripheral VSDs. Conformational changes in the VSDs in response to membrane depolarization are transmitted to the PMs through the S4-S5 linkers (identified by arrows through the helices). *Reprinted by permission from Nature: Dib-Hajj SD, Yang Y, Black JA, et al. The $\text{Na}_V1.7$ sodium channel: from molecule to man. Nat Rev Neurosci. 2013;14(1):49-62. Copyright © 2012 Springer Nature.*

Frequency-Dependent Blockade

Sodium ion channels tend to recover from local anesthetic-induced conduction blockade between action potentials and to develop additional conduction blockade each time sodium channels open during an action potential (frequency-dependent blockade). Therefore, local anesthetic molecules can gain access to receptors only when sodium channels are in activated-open states. For this reason, selective conduction blockade of nerve fibers by local anesthetics may be related to the nerve's characteristic frequencies of activity as well as to its anatomic properties, such as diameter. Indeed, a resting nerve is less sensitive to local anesthetic-induced conduction blockade than is a nerve that has been repetitively stimulated. The pharmacologic effects of other drugs, including anticonvulsants and barbiturates in addition to local anesthetics, may reflect frequency-dependent blockade (see [Chapter 13](#)).

Other Site of Action Targets

In addition to sodium ion channels, local anesthetics block voltage-dependent potassium ion channels. Compared with sodium ion channels, local anesthetics exhibit a much lower affinity. However, blockade of

potassium ion channels might explain broadening of the action potential in the presence of local anesthetics. Considering the structural similarity between voltage-dependent calcium ion channels and sodium ion channels, it is not surprising that calcium ion currents (L-type most sensitive) may also be blocked by local anesthetics.¹⁵ Although local anesthetics are considered principally ion channel blockers, there is evidence these drugs may also act on G protein-coupled receptors.¹⁶

Minimum Effective Concentration

The minimum concentration of local anesthetic necessary to produce conduction blockade of nerve impulses is termed the **C_m**. The C_m is analogous to the minimum alveolar concentration for inhaled anesthetics. Nerve fiber diameter influences C_m, with larger nerve fibers requiring higher concentrations of local anesthetic for production of conduction blockade. An increased tissue pH or high frequency of nerve stimulation decreases C_m.

Each local anesthetic has a unique C_m, reflecting differing potencies of each drug. The C_m of motor fibers is approximately twice that of sensory fibers; thus, sensory anesthesia may not always be accompanied by skeletal muscle paralysis. Despite an unchanged C_m, less local anesthetic is needed for subarachnoid anesthesia than for epidural anesthesia, reflecting greater access of local anesthetics to unprotected nerves in the subarachnoid space.

Peripheral nerves are composed of myelinated A and B fibers and nonmyelinated C fibers. A minimal length of myelinated nerve fiber must be exposed to an adequate concentration of local anesthetic for conduction blockade of nerve impulses to occur. For example, if only one node of Ranvier is blocked (site of change in sodium permeability), the nerve impulse can jump (skip) across this node and conduction blockade does not occur. For conduction blockade to occur in an A fiber, it is necessary to expose at least two and preferably three successive nodes of Ranvier (approximately 1 cm) to an adequate concentration of local anesthetic. Both types of pain-conducting fibers (myelinated A-δ and nonmyelinated C fibers) are blocked by similar concentrations of local anesthetics despite the differences in the diameters of these fibers.

Preganglionic B fibers are more readily blocked by local anesthetics than any fiber, even though these fibers are myelinated.

Differential Conduction Blockade

Differential conduction blockade is illustrated by selective blockade of preganglionic sympathetic nervous system B fibers using low concentrations of local anesthetics. Slightly higher concentrations of local anesthetics interrupt conduction in small C fibers and small- and medium-sized A fibers, with loss of sensation for pain and temperature. Nevertheless, touch, proprioception, and motor function are still present such that the patient will sense pressure but not pain with surgical stimulation. In an anxious patient, however, any sensation may be misinterpreted as failure of the local anesthetic.

Pharmacokinetics

Local anesthetics are weak bases that have pK values somewhat above physiologic pH (see **Table 10.1**). As a result, <50% of the local anesthetic exists in a lipid-soluble nonionized form at physiologic pH. For example, at pH 7.4, only 5% of tetracaine exists in a nonionized form. Acidosis in the environment into which the local anesthetic is injected (as is present with tissue infection) further increases the ionized fraction of drug. This is consistent with the poor quality of local anesthesia that often results when a local anesthetic is injected into an acidic infected area. Local anesthetics with pKs nearest to physiologic pH have the most rapid onset of action, reflecting the presence of an optimal ratio of ionized to nonionized drug fraction (see **Table 10.1**).

Intrinsic vasodilator activity will also influence apparent potency and duration of action. For example, the enhanced vasodilator action of lidocaine compared with mepivacaine results in the greater systemic absorption and shorter duration of action of lidocaine. Bupivacaine and etidocaine produce similar vasodilation, but plasma concentrations of bupivacaine after epidural placement exceed those of etidocaine.

Absorption and Distribution

Absorption of a local anesthetic from its site of injection into the systemic circulation is influenced by the site of injection and dosage, use of epinephrine, and pharmacologic characteristics of the drug ([Figure 10.5](#)). The ultimate plasma concentration of a local anesthetic is determined by the rate of tissue distribution and the rate of clearance of the drug. For example, the infusion of lidocaine for 1 minute is followed by a rapid decrease in the drug's plasma concentration that is paralleled by an initial high uptake into the lungs and distribution of the local anesthetic to highly perfused tissues (brain, heart, and kidneys).¹⁷ Lipid solubility of the local anesthetic is important in this redistribution as well as being a primary determinant of intrinsic local anesthetic potency. After distribution to highly perfused tissues, the local anesthetic is redistributed to less well-perfused tissues, including skeletal muscles and fat. Consideration of cardiac output is important for describing the overall tissue distribution of local anesthetics and presumably their intercompartmental clearance.¹⁸ Ultimately, the local anesthetic is eliminated from the plasma by metabolism and excretion.

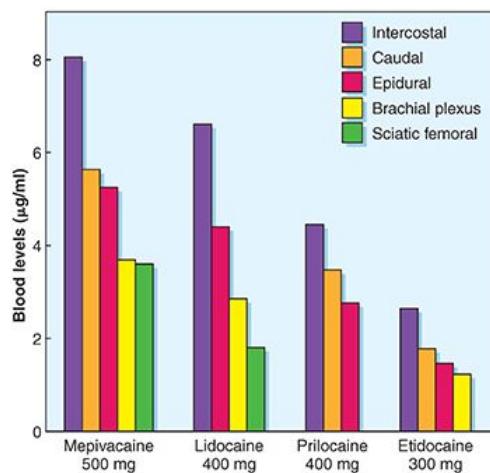


FIGURE 10.5 Peak plasma concentrations of local anesthetic are influenced by the site of injection for accomplishment of regional anesthesia.

In addition to the tissue blood flow and lipid solubility of the local anesthetic, patient-related factors such as age, cardiovascular status, and hepatic function will also influence the absorption and resultant plasma concentrations of local anesthetics. Protein binding of local anesthetics will influence their distribution and excretion. In this regard, protein binding parallels lipid solubility of the local anesthetic and is inversely related to the plasma concentration of drug ([Figure 10.6](#); see [Table 10.1](#)).¹⁹ Overall, after systemic absorption, amide local anesthetics are more widely distributed in tissues than ester local anesthetics.

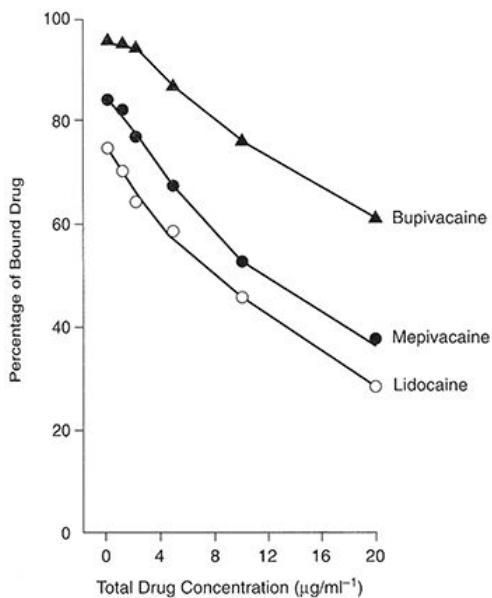


FIGURE 10.6 The percentage of local anesthetic bound to protein is inversely related to the plasma concentration of drug. Reprinted with permission from Tucker GT, Boyes RN, Bridenbaugh PO, et al. Binding of anilide-type local anesthetics in human plasma: I. Relationships between binding, physiochemical properties, and anesthetic activity. *Anesthesiology*. 1970;33(3):287-303. Copyright © 1970 American Society of Anesthesiologists, Inc.

Lung Extraction

The lungs are capable of extracting local anesthetics such as lidocaine, bupivacaine, and prilocaine from the circulation.²⁰ After rapid entry of local anesthetics into the venous circulation, this pulmonary extraction will limit the concentration of drug that reaches the systemic circulation for distribution to the coronary and cerebral circulations. For bupivacaine, this first-pass pulmonary extraction is dose dependent, suggesting that the uptake process becomes saturated rapidly.²¹ Propranolol impairs bupivacaine extraction by the lungs, perhaps reflecting a common receptor site for the two drugs.²² Furthermore, propranolol decreases plasma clearance of lidocaine and bupivacaine, presumably reflecting propranolol-induced decreases in hepatic blood flow or inhibition of hepatic metabolism.²³

Changes During Pregnancy (see also Chapter 45)

Increased sensitivity (more rapid onset of conduction blockade) may be present during pregnancy.²⁴ Alterations in protein-binding characteristics of bupivacaine may result in increased concentrations of pharmacologically active unbound drug in the parturient's plasma.²⁵ Nevertheless, progesterone, which binds to the same α_1 -acid glycoprotein as bupivacaine, does not influence protein binding of this local anesthetic.²⁵ This evidence suggests that bupivacaine and progesterone bind to discrete but separate sites on protein molecules.

Placental Transfer

There may be clinically significant transplacental transfer of local anesthetics between the mother and fetus. Plasma protein binding influences the rate and degree of diffusion of local anesthetics across the placenta (see **Table 10.1**). Bupivacaine, which is highly protein bound (approximately 95%), has an umbilical vein-maternal arterial concentration ratio of about 0.32 compared with a ratio of 0.73 for lidocaine (approximately 70% protein bound) and a ratio of 0.85 for prilocaine (approximately 55% protein bound).²⁶ Ester local anesthetics, because of their rapid hydrolysis, are not available to cross the placenta in significant amounts.

Acidosis in the fetus, which may occur during prolonged labor, can result in accumulation of local anesthetic molecules in the fetus (ion trapping) ([Figure 10.7](#)).²⁷

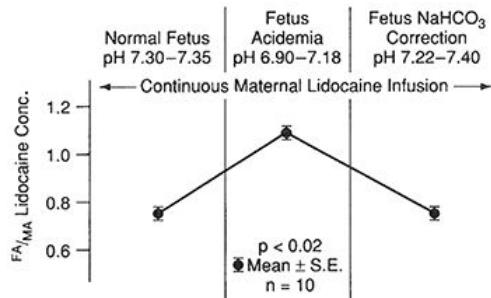


FIGURE 10.7 Fetal-maternal arterial (FA/MA) lidocaine ratios are greater during acidemia compared with a normal pH. *Reprinted with permission from Biehl D, Shnider SM, Levinson G, et al. Placental transfer of lidocaine: effects of fetal acidosis. Anesthesiology. 1978;48(6):409-412. Copyright © 1978 American Society of Anesthesiologists, Inc.*

Renal Elimination and Clearance

The poor water solubility of local anesthetics usually limits renal excretion of unchanged drug to <5%.²⁸ The exception is cocaine, of which 10% to 12% of unchanged drug can be recovered in urine. Water-soluble metabolites of local anesthetics, such as para-aminobenzoic acid resulting from metabolism of ester local anesthetics, are readily excreted in urine. Clearance values and elimination half-times for amide local anesthetics probably represent mainly hepatic metabolism because renal excretion of unchanged drug is minimal (see [Table 10.1](#)). Pharmacokinetic studies of ester local anesthetics are limited because of a short elimination half-time due to their rapid hydrolysis in the plasma by esterases.

Metabolism of Amide Local Anesthetics

Amide local anesthetics undergo varying rates of metabolism by microsomal enzymes located primarily in the liver. Prilocaine undergoes the most rapid metabolism; lidocaine and mepivacaine are intermediate; and etidocaine, bupivacaine, and ropivacaine undergo the slowest metabolism among the amide local anesthetics. The initial step is conversion of the amide base to aminocarboxylic acid and a cyclic aniline derivative. Complete metabolism usually involves additional steps, such as hydroxylation of the aniline moiety and *N*-dealkylation of the aminocarboxylic acid.

Compared with that of ester local anesthetics, the metabolism of amide local anesthetics is more complex and slower. This slower metabolism means that sustained increases of the plasma concentrations of amide local anesthetics, and thus systemic toxicity, are more likely than with ester local anesthetics. Furthermore, cumulative drug effects of amide local anesthetics are more likely than with ester local anesthetics.

Lidocaine

The principal metabolic pathway of lidocaine is oxidative dealkylation in the liver to monoethylglycinexylidide followed by hydrolysis of this metabolite to xylidide. Monoethylglycinexylidide has approximately 80% of the activity of lidocaine for protecting against cardiac dysrhythmias in an animal model. This metabolite has a prolonged elimination half-time, accounting for its efficacy in controlling cardiac dysrhythmias after the infusion of lidocaine is discontinued. Xylidide has only approximately 10% of the cardiac antidysrhythmic activity of lidocaine. In humans, approximately 75% of xylidide is excreted in the urine as 4-hydroxy-2,6-dimethylaniline.

Hepatic disease or decreases in hepatic blood flow, which may occur during anesthesia, can decrease the rate of metabolism of lidocaine. For example, the elimination half-time of lidocaine is increased more than fivefold in patients with liver dysfunction compared with normal patients. Decreased hepatic metabolism of

lidocaine should be anticipated when patients are anesthetized with volatile anesthetics. Maternal clearance of lidocaine is prolonged in the presence of pregnancy-induced hypertension, and repeated administration of lidocaine can result in higher plasma concentrations than in normotensive parturients.²⁹ Lidocaine has intrinsic vasodilator property.³⁰

Prilocaine

Prilocaine is an amide local anesthetic that is metabolized to ortho-toluidine. Ortho-toluidine is an oxidizing compound capable of converting hemoglobin to its oxidized form, methemoglobin, resulting in a potentially life-threatening complication, methemoglobinemia (see “[Methemoglobinemia](#)” section). When the dose of prilocaine is >600 mg, there may be sufficient methemoglobin present (3-5 g/dL) to cause the patient to appear cyanotic, and oxygen-carrying capacity is decreased. Methemoglobinemia is readily reversed by the administration of methylene blue, 1 to 2 mg/kg intravenously (IV), over 5 minutes (total dose should not exceed 7-8 mg/kg). The ability of prilocaine to cause dose-related methemoglobinemia limits its clinical usefulness, with the exception of IV regional anesthesia. Prilocaine causes less vasodilation than other local anesthetics and thus can be used without epinephrine added to the local anesthetic solution.

Mepivacaine

Mepivacaine has pharmacologic properties similar to those of lidocaine, although the duration of action of mepivacaine is somewhat longer. Clearance of mepivacaine is decreased in neonates, leading to a prolonged elimination half-time. In contrast to lidocaine, mepivacaine has limited vasodilator activity. As such, mepivacaine is an alternate selection when addition of epinephrine to the local anesthetic solution is not recommended.

Bupivacaine

Possible pathways for metabolism of bupivacaine include aromatic hydroxylation, *N*-dealkylation, amide hydrolysis, and conjugation.³¹ Only the *N*-dealkylated metabolite *N*-desbutylbupivacaine, has been measured in blood or urine after epidural or spinal anesthesia. The mean total urinary excretion of bupivacaine and its dealkylation and hydroxylation metabolites account for >40% of the total anesthetic dose.³¹ α_1 -Acid glycoprotein is the most important plasma protein binding site of bupivacaine, and its concentration is increased in many clinical situations, including postoperative trauma.³²

Ropivacaine

Ropivacaine is metabolized to 2,6-pipercoloxylidide and 3-hydroxyropivacaine by hepatic cytochrome P-450 enzymes. Both metabolites have significantly less local anesthetic potency than ropivacaine. Because only a very small fraction of ropivacaine is excreted unchanged in the urine (about 1%) when the liver is functioning normally, dosage adjustments based on renal function do not seem necessary. However, in uremic patients, 2,6-pipercoloxylidide may accumulate and produce toxic effects.³³ Overall, clearance of ropivacaine is higher than that determined for bupivacaine, and its elimination half-time is shorter.⁵ The higher clearance of ropivacaine may offer an advantage over bupivacaine in terms of systemic toxicity. The lipid solubility of ropivacaine is intermediate between lidocaine and bupivacaine. Ropivacaine is highly bound to α_1 -acid glycoprotein.

Dibucaine

Dibucaine is a quinoline derivative with an amide bond in the connecting hydrocarbon chain. This local anesthetic is metabolized in the liver and is the most slowly eliminated of all the amide derivatives. Interestingly, dibucaine inhibits pseudocholinesterase and is used to differentiate individuals who have substitution mutations of the plasma cholinesterase enzyme.³⁴ The dibucaine number is the percentage of plasma cholinesterase enzyme inhibited by dibucaine. A normal enzyme will be 80% inhibited by dibucaine, whereas an abnormal enzyme will be 20% inhibited.³⁵

Metabolism of Ester Local Anesthetics

Ester local anesthetics undergo hydrolysis by cholinesterase enzyme, principally in the plasma and to a lesser extent in the liver. The rate of hydrolysis varies, with chloroprocaine being most rapid, procaine being intermediate, and tetracaine being the slowest. The resulting metabolites are pharmacologically inactive, although para-aminobenzoic acid may be an antigen responsible for subsequent allergic reactions. The exception to hydrolysis of ester local anesthetics in the plasma is cocaine, which undergoes significant metabolism in the liver.

Systemic toxicity is inversely proportional to the rate of hydrolysis; thus, tetracaine is more likely than chloroprocaine to result in excessive plasma concentrations. Because cerebrospinal fluid contains little to no cholinesterase enzyme, anesthesia produced by subarachnoid placement of tetracaine will persist until the drug has been absorbed into the systemic circulation. Plasma cholinesterase activity and the hydrolysis rate of ester local anesthetics are slowed in the presence of liver disease or an increased blood urea nitrogen concentration. Plasma cholinesterase activity may be decreased in parturients and in patients being treated with certain chemotherapeutic drugs. Patients with atypical plasma cholinesterase may be at increased risk for developing excess systemic concentrations of an ester local anesthetic due to absent or limited plasma hydrolysis.

Procaine

Procaine is hydrolyzed to para-aminobenzoic acid, which is excreted unchanged in urine, and to diethylaminoethanol, which is further metabolized because only 30% is recovered in urine. Overall, <50% of procaine is excreted unchanged in urine. Increased plasma concentrations of para-aminobenzoic acid do not produce symptoms of systemic toxicity.

Chloroprocaine

Addition of a chlorine atom to the benzene ring of procaine to form chloroprocaine increases by 3.5 times the rate of hydrolysis of the local anesthetic by plasma cholinesterase, as compared with procaine. Resulting pharmacologically inactive metabolites of chloroprocaine are 2-chloro-aminobenzoic acid and 2-diethylaminoethanol. Maternal and neonatal plasma cholinesterase activity may be decreased up to 40% at term, but minimal placental passage of chloroprocaine confirms that even this decreased activity is adequate to hydrolyze most of the chloroprocaine that is absorbed from the maternal epidural space.^{36,37}

Tetracaine

Tetracaine undergoes hydrolysis by plasma cholinesterase, but the rate is slower than for procaine.

Benzocaine

Benzocaine (ethyl aminobenzoate) is unique among clinically useful local anesthetics because it is a weak acid (pK_a 3.5) so that it exists only in the nonionized form at physiologic pH. As such, benzocaine is ideally suited for topical anesthesia of mucous membranes prior to tracheal intubation, endoscopy, transesophageal echocardiography, and bronchoscopy. Onset of topical anesthesia is rapid and lasts 30 to 60 minutes. A brief spray of 20% benzocaine delivers the recommended dose of 200 to 300 mg. Systemic absorption of topical benzocaine is enhanced by defects in the skin and mucosa as well as from the gastrointestinal tract should any of the local anesthetic be swallowed. Cetacaine is a combination of 14% benzocaine, 2% tetracaine, and 2% butamben. Methemoglobinemia is a rare but potentially life-threatening complication following topical application of benzocaine, especially when the dose exceeds 200 to 300 mg (see “[Methemoglobinemia](#)” section).

Cocaine

Cocaine is metabolized by plasma and liver cholinesterases to water-soluble metabolites that are excreted in urine. Plasma cholinesterase activity is decreased in parturients, neonates, the elderly, and patients with severe underlying hepatic disease. Cocaine may be present in urine for 24 to 36 hours, depending on the route

of administration and cholinesterase activity. Assays for the metabolites of cocaine in urine are useful markers of cocaine use or absorption (see “[Cocaine Toxicity](#)” section).

Alkalization of Local Anesthetic Solutions

Alkalization of local anesthetic solutions shortens the onset of neural blockade, enhances the depth of sensory and motor blockade, and increases the spread of epidural blockade.³⁸ The pH of commercial preparations of local anesthetic solutions ranges from 3.9 to 6.5 and is especially acidic if prepackaged with epinephrine (increased acidity prolongs the shelf life of epinephrine). The pKa of local anesthetics used clinically is near 8 so that only a small fraction (about 3%) of the local anesthetic exists in the lipid-soluble form. Alkalization increases the percentage of local anesthetic existing in the lipid-soluble form that is available to diffuse across lipid cellular barriers. Adding sodium bicarbonate will speed the onset of peripheral nerve block and epidural block by 3 to 5 minutes.

Adjvant Mixed With Local Anesthetics

Dexmedetomidine has been used as an adjvant in local anesthetic admixtures, and the central effect is postulated for prolongation of the local anesthetic affect. The IV dexmedetomidine, in a recent systematic review and meta-analysis, showed increased duration of motor and sensory block after spinal anesthesia and time to first analgesic request was increased.³⁹ Magnesium has also shown promising initial results when introduced in intrathecal space as an addition to local anesthetic with or without opioids. Duration of spinal anesthesia was increased in magnesium group.⁴⁰ In pediatric patients, addition of clonidine and ketamine to the locoregional anesthesia showed good pharmacokinetic and pharmacodynamic profiles of efficacy and safety, improving and prolonging the action of associated local anesthetics.⁴¹

Combinations of Local Anesthetics

Local anesthetics may be combined in an effort to produce a rapid onset (chloroprocaine) and prolonged duration (bupivacaine) of action. Nevertheless, placement of chloroprocaine in the epidural space may decrease the efficacy of subsequent epidural bupivacaine-induced analgesia during labor. It is speculated that the low pH of the chloroprocaine solution could decrease the nonionized pharmacologically active fraction of bupivacaine.⁴² Tachyphylaxis to the local anesthetic mixture could also reflect local acidosis due to the low pH of the bathing solution. For these reasons, adjustment of the pH of the chloroprocaine solution with the addition of 1 mL of 8.4% sodium bicarbonate added to 30 mL of chloroprocaine solution just before placement into the epidural space may improve the efficacy of the chloroprocaine-bupivacaine combination.⁴³ Local anesthetic toxicity of combinations of drugs is additive rather than synergistic.⁴⁴

Use of Vasoconstrictors

The duration of action of a local anesthetic is proportional to the time the drug is in contact with nerve fibers. For this reason, epinephrine (1:200,000 or 5 µg/mL) may be added to local anesthetic solutions to produce vasoconstriction, which limits systemic absorption and maintains the drug concentration in the vicinity of the nerve fibers to be anesthetized. Indeed, addition of epinephrine to a lidocaine or mepivacaine solution prolongs the duration of conduction blockade and decreases systemic absorption of local anesthetics by 20% to 30% ([Figure 10.8](#)).^{45,46} For bupivacaine, addition of epinephrine also increases the duration of conduction blockade but to a lesser degree, and the reduction in systemic absorption is by 10% to 20%. Most local anesthetics, with the exception of ropivacaine, possess intrinsic vasodilator properties, and it is possible that epinephrine-induced vasoconstriction will slow clearance from the injection site, thus prolonging the time the drug is in contact with nerve fibers.

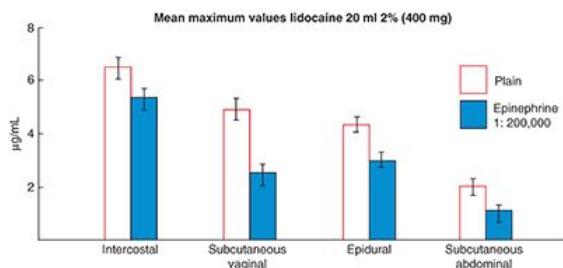


FIGURE 10.8 Addition of epinephrine to the solution containing lidocaine or prilocaine decreases systemic absorption of the local anesthetic by about one-third. *Reprinted from Scott DB, Jebson PJ, Braid DP, et al. Factors affecting plasma levels of lignocaine and prilocaine. Br J Anaesth. 1972;44(10):1040-1049.* Copyright © 1972 Elsevier. With permission.

The impact of adding epinephrine to the local anesthetic solution is influenced by the specific local anesthetic selected and the level of sensory blockade required if a spinal or epidural anesthetic is chosen. For example, the impact of epinephrine in prolonging the duration of conduction blockade and decreasing systemic absorption of bupivacaine and etidocaine is less than that observed with lidocaine, presumably because the greater lipid solubility of bupivacaine and etidocaine causes them to bind avidly to tissues. The duration of sensory anesthesia in the lower extremities, but not the abdominal region, is extended when epinephrine (0.2 mg) or phenylephrine (2 mg) is added to local anesthetic solutions of bupivacaine or lidocaine placed into the subarachnoid space. Vasoconstrictors prolong the effect of tetracaine for spinal anesthesia. Epinephrine added to a low dose of tetracaine (6 mg) increases the success rate of spinal anesthesia, whereas the success rate is not altered by epinephrine when the subarachnoid dose of tetracaine is 10 mg.⁴⁷ In addition to decreasing systemic absorption to prolong conduction blockade, epinephrine may also enhance conduction blockade by increasing neuronal uptake of the local anesthetic. The α -adrenergic effects of epinephrine may be associated with some degree of analgesia that could contribute to the effects of the conduction blockade. The addition of epinephrine to local anesthetic solutions has little, if any, effect on the onset rate of local anesthesia.

Decreased systemic absorption of local anesthetic due to vasoconstriction produced by epinephrine increases the likelihood that the rate of metabolism will match that of absorption, thus decreasing the possibility of systemic toxicity. Systemic absorption of epinephrine may accentuate systemic hypertension in vulnerable patients.

Adverse Effects of Local Anesthetics

The principal side effects related to the use of local anesthetics are allergic reactions and systemic toxicity due to excessive plasma and tissue concentrations of the local anesthetic. Systemic toxicity in association with regional anesthesia is estimated to result in seizures in 1 to 4 per 1,000 patient exposures to local anesthetics, with bupivacaine being the drug most likely to be associated with this adverse response.⁴⁸ In orthopedic patients receiving peripheral nerve blocks, 0.18% of patients suffered local anesthetic systemic toxicity (LAST) or surrogate outcomes including cardiac arrest, seizures, and use of lipid emulsion on the day of surgery.⁴⁹

Allergic Reactions

Allergic reactions to local anesthetics are rare despite the frequent use of these drugs. It is estimated that less than 1% of all adverse reactions to local anesthetics are due to an allergic mechanism.⁵⁰ Instead, the overwhelming majority of adverse responses that are often attributed to an allergic reaction are instead manifestations of excess plasma concentrations of the local anesthetic.

Esters of local anesthetics that produce metabolites related to para-aminobenzoic acid are more likely than amide local anesthetics, which are not metabolized to para-aminobenzoic acid, to evoke an allergic reaction. An allergic reaction after the use of a local anesthetic may be due to methylparaben or similar substances used as preservatives in commercial preparations of ester and amide local anesthetics. These

preservatives are structurally similar to para-aminobenzoic acid. As a result, an allergic reaction may reflect prior stimulation of antibody production by the preservative and not a reaction to the local anesthetic.

Cross-Sensitivity

Cross-sensitivity between local anesthetics reflects the common metabolite para-aminobenzoic acid. A similar cross-sensitivity, however, does not exist between classes of local anesthetics. Therefore, a patient with a known allergy to an ester local anesthetic can receive an amide local anesthetic without an increased risk of an allergic reaction. Likewise, an ester local anesthetic can be administered to a patient with a known allergy to an amide local anesthetic. It is important that the “safe” local anesthetic be preservative free.

Documentation of Allergy

Documentation of allergy to a local anesthetic is based on the clinical history and perhaps the use of intradermal testing. The occurrence of rash, urticaria, and laryngeal edema, with or without hypotension and bronchospasm, is highly suggestive of a local anesthetic-induced allergic reaction. Conversely, hypotension associated with syncope or tachycardia when an epinephrine-containing local anesthetic solution is administered suggests an accidental intravascular injection of drug. Use of an intradermal test requires injection of preservative-free preparations of local anesthetic solutions to eliminate the possibility that the allergic reaction was caused by a substance other than the local anesthetic.

Local Anesthetic Systemic Toxicity

The LAST is due to an excess plasma concentration of the drug. Plasma concentrations of local anesthetics are determined by the rate of drug entrance into the systemic circulation relative to their redistribution to inactive tissue sites and clearance by metabolism. Accidental direct intravascular injection of local anesthetic solutions during performance of peripheral nerve block anesthesia or epidural anesthesia is the most common mechanism for production of excess plasma concentrations of local anesthetics. A variety of factors influence the likelihood and severity of LAST, including individual patient risk factors, concurrent medications, location and technique of block, specific local anesthetic compound, total local anesthetic dose (the product of concentration and volume), timeliness of detection, and adequacy of treatment.⁵¹ The magnitude of this systemic absorption depends on the (1) dose administered into the tissues, (2) vascularity of the injection site, (3) presence of epinephrine in the solution, and (4) physicochemical properties of the drug (see [Table 10.1](#)). For example, systemic absorption of local anesthetics is greatest after injection for an intercostal nerve block, intermediate for epidural anesthesia, and least for a brachial plexus block.⁵² Addition of 5 µg of epinephrine to every milliliter of local anesthetic solution (1:200,000 dilution) decreases systemic absorption of local anesthetics by approximately one-third (see “[Use of Vasoconstrictors](#)”).⁴⁶ Systemic toxicity of local anesthetics involves the CNS and cardiovascular system.

Local anesthetics differ with regard to their CNS toxicity and cardiac toxicity. The cardiovascular system/CNS ratio describes the dose required to produce cardiovascular arrhythmias versus that required to produce seizures.⁵³ If the ratio is lower, it implies a reduced safety margin for the local anesthetic compounds compared to the compound with higher ratio to detect impending cardiotoxicity based on premonitory CNS signs. Bupivacaine is a more potent local anesthetic and generates arrhythmias at lower concentrations compared with lidocaine and mepivacaine. Also in animal studies (dogs), at comparable dosages, bupivacaine and etidocaine caused severe arrhythmias without decreased contractility, whereas lidocaine caused the opposite, that is, depressed myocardial contractility without arrhythmia.⁵⁴

Central Nervous System Effects

Low plasma concentrations of local anesthetics are likely to produce numbness of the tongue and circumoral tissues, presumably reflecting delivery of drug to these highly vascular tissues ([Table 10.2](#)). As the plasma concentrations continue to increase, local anesthetics readily cross the blood–brain barrier and produce a predictable pattern of CNS changes. Restlessness, vertigo, tinnitus, and difficulty in focusing occur initially. Further increases in the CNS concentration of local anesthetic result in slurred speech and skeletal muscle twitching. Skeletal muscle twitching is often first evident in the face and extremities and signals the

imminence of tonic-clonic seizures. Vivid fear of imminent death and a delusional belief of having died have been described in patients experiencing toxic reactions to local anesthetics administered for regional anesthesia and pain relief.⁵⁵

TABLE 10.2

Dose-dependent effects of lidocaine

Plasma lidocaine concentration ($\mu\text{g}/\text{mL}$)	Effect
1-5	Analgesia
5-10	Circumoral numbness Tinnitus Skeletal muscle twitching Systemic hypotension Myocardial depression
10-15	Seizures Unconsciousness
15-25	Apnea Coma
>25	Cardiovascular depression

Lidocaine and other amide local anesthetics may cause drowsiness before the onset of seizures. Seizures are classically followed by CNS depression, which may be accompanied by hypotension and apnea. The onset of seizures may reflect selective depression of inhibitory cortical neurons by local anesthetics, leaving excitatory pathways unopposed. An alternative explanation for seizures is local anesthetic-induced inhibition of the release of neurotransmitters, particularly γ -aminobutyric acid. The precise site of local anesthetic-induced seizures is not known, although it appears to be in the temporal lobe or the amygdala.

Plasma concentrations of local anesthetics producing signs of CNS toxicity depend on the specific drug involved. Lidocaine, mepivacaine, and prilocaine demonstrate effects on the CNS at plasma concentrations of 5 to 10 $\mu\text{g}/\text{mL}$. The typical plasma concentration of bupivacaine associated with seizures is 4.5 to 5.5 $\mu\text{g}/\text{mL}$.^{52,56} Ropivacaine and bupivacaine produce convulsions in awake animals at similar doses.⁵ The threshold plasma concentration at which CNS toxicity occurs may be related more to the rate of increase of the serum concentration than to the total amount of drug injected.²⁸

The active metabolites of lidocaine, including monoethylglycinexylidide, may exert an additive effect in causing systemic toxicity after epidural administration of lidocaine. For this reason, it has been recommended that the plasma venous concentration of lidocaine be monitored when the cumulative epidural dose of lidocaine is >900 mg.⁵⁷ The seizure threshold for lidocaine may be related to CNS levels of serotonin (5-hydroxytryptophan). For example, accumulation of serotonin decreases the seizure threshold of lidocaine and prolongs the duration of seizure activity.

There is an inverse relationship between the Paco_2 and seizure thresholds of local anesthetics, presumably reflecting variations in cerebral blood flow and resultant delivery of drugs to the brain. Increases in the serum potassium concentration can facilitate depolarization and thus markedly increase local anesthetic toxicity. Conversely, hypokalemia, by creating hyperpolarization, can greatly decrease local anesthetic toxicity. The threshold for neurotoxicity of lidocaine may be decreased when patients being treated with the antidysrhythmic drug mexiletine receive lidocaine during the perioperative period,⁵⁸ presumably by displacement of lidocaine from tissue binding sites.⁵⁹

Cardiovascular System Effects

The cardiovascular system is more resistant to the toxic effects of high plasma concentrations of local anesthetics than is the CNS. For example, lidocaine in plasma concentrations of <5 $\mu\text{g}/\text{mL}$ is devoid of adverse cardiac effects, producing only a decrease in the rate of spontaneous phase 4 depolarization (automaticity). Nevertheless, plasma lidocaine concentrations of 5 to 10 $\mu\text{g}/\text{mL}$, and equivalent plasma

concentrations of other local anesthetics, may produce profound hypotension due to relaxation of arteriolar vascular smooth muscle and direct myocardial depression (see [Table 10.2](#)). As a result, hypotension reflects both decreased systemic vascular resistance and cardiac output.

Part of the cardiac toxicity that results from high plasma concentrations of local anesthetics occurs because these drugs also block cardiac sodium channels. At low concentrations of local anesthetics, this effect on sodium channels probably contributes to cardiac antidysrhythmic properties of these drugs. However, when the plasma concentrations of local anesthetics are excessive, sufficient cardiac sodium channels become blocked so that conduction and automaticity become adversely depressed. For example, excessive plasma concentrations of lidocaine may slow conduction of cardiac impulses through the heart, manifesting as prolongation of the P-R interval and QRS complex on the electrocardiogram. Effects of local anesthetics on calcium ion and potassium ion channels and local anesthetic-induced inhibition of cyclic adenosine monophosphate production may also contribute to cardiac toxicity.⁶⁰

Selective Cardiac Toxicity

Accidental IV injection of bupivacaine may result in precipitous hypotension, cardiac dysrhythmias, and atrioventricular heart block.⁶¹ After accidental IV injection, the protein-binding sites (α_1 -acid glycoprotein and albumin) for bupivacaine are quickly saturated, leaving a significant mass of unbound drug available for diffusion into the conducting tissue of the heart. The IV injection of bupivacaine or lidocaine to awake animals produces serious cardiac dysrhythmias only in animals receiving bupivacaine. Premature ventricular contractions, wide QRS complexes, and ventricular tachycardia are most common arrhythmias seen, although other arrhythmias like supraventricular tachycardia, atrioventricular heart block, and ST-T wave changes can also occur but at lesser rate.⁶² Cardiotoxic plasma concentrations of bupivacaine are 8 to 10 $\mu\text{g}/\text{mL}$.⁶³

Physiologic changes and concomitant drug therapy may make patients more vulnerable to bupivacaine cardiac toxicity. For example, pregnancy may increase sensitivity to cardiotoxic effects of bupivacaine, but not ropivacaine, as emphasized by occurrence of cardiopulmonary collapse with a smaller dose of bupivacaine in pregnant compared with nonpregnant animals ([Figure 10.9](#)).^{5,64} The threshold for cardiac toxicity produced by bupivacaine may be decreased in patients being treated with drugs that inhibit myocardial impulse propagation (β -adrenergic blockers, digitalis preparations, calcium channel blockers).⁶⁵ Indeed, in the presence of propranolol, atrioventricular heart block and cardiac dysrhythmias occurred at plasma bupivacaine concentrations of 2 to 3 $\mu\text{g}/\text{mL}$.⁶³ This suggests that caution must be taken in the use of bupivacaine in patients who are on antidysrhythmic drugs or other cardiac medications known to depress impulse propagation. Inhibition of basal and epinephrine-stimulated cyclic adenosine monophosphate production by bupivacaine may limit the success of resuscitative measures using epinephrine administered for bupivacaine cardiovascular toxicity.⁶⁶ The cardiac toxicity of bupivacaine in animals is enhanced by arterial hypoxemia, acidosis, or hypercarbia.

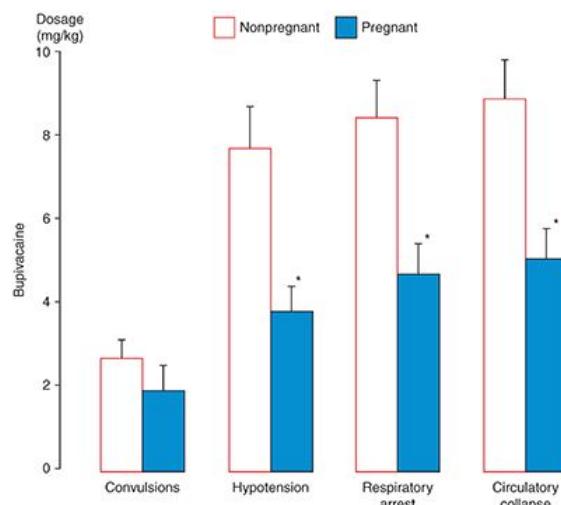


FIGURE 10.9 The dose of bupivacaine required to evoke toxic effects is less in pregnant than in nonpregnant ewes (mean \pm standard error; $*P < .05$). Reprinted with permission from Morishima HO, Pedersen H, Finster M, et al. Bupivacaine toxicity in pregnant and nonpregnant ewes. *Anesthesiology*. 1985;63(2):134-139. Copyright © 1985 American Society of Anesthesiologists, Inc.

All local anesthetics depress the maximal depolarization rate of the cardiac action potential (V_{max}) by virtue of their ability to inhibit sodium ion influx via sodium channels. In isolated papillary muscle preparations, bupivacaine depresses V_{max} considerably more than lidocaine, whereas ropivacaine is intermediate in its depressant effect on V_{max} (Figure 10.10).^{5,67} The resulting slowed conduction of the cardiac action potential manifests on the electrocardiogram as prolongation of the P-R and QRS intervals and reentry ventricular cardiac dysrhythmias. Both bupivacaine and lidocaine block cardiac sodium ion channels during systole, whereas during diastole, highly lipid soluble bupivacaine dissociates off these channels at a slow rate compared with lidocaine, thus accounting for the drug's persistent depressant effect on V_{max} and subsequent cardiac toxicity.⁶⁸ At normal heart rates, diastolic time is sufficiently long for lidocaine dissociation, but bupivacaine block intensifies and depresses electrical conduction, causing reentrant-type ventricular dysrhythmias. Less lipid-soluble lidocaine dissociates rapidly from cardiac sodium channels and cardiac toxicity is low. Furthermore, high plasma concentrations of bupivacaine may cause ventricular cardiac dysrhythmias through a direct brainstem effect. The R enantiomer of bupivacaine is more toxic than the S enantiomer. For example, seizure activity following an interscalene block with levobupivacaine was not associated with cardiac dysrhythmias or other signs of cardiovascular toxicity.⁶⁹ In animals, levobupivacaine compared with bupivacaine was associated with a lower incidence of ventricular cardiac dysrhythmias, and successful resuscitation was more likely in the presence of levobupivacaine.^{70,71} Ropivacaine is a pure S enantiomer that is less lipid soluble and less cardiotoxic than bupivacaine but more cardiotoxic than lidocaine.^{2,72} Although ropivacaine-induced cardiac arrest has been described following peripheral nerve block anesthesia, in contrast to bupivacaine, cardiac resuscitation is more likely to be successful.⁷³⁻⁷⁵

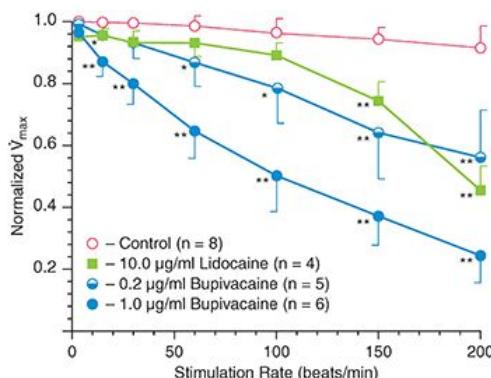


FIGURE 10.10 In an isolated papillary muscle preparation, maximum upstroke velocity of action potential is depressed more by bupivacaine than by lidocaine (* $P < .05$; ** $P < .01$). Reprinted with permission from Clarkson CW, Hondeghem LM. Mechanism for bupivacaine depression of cardiac conduction: fast block of sodium channels during the action potential with slow recovery from block during diastole. *Anesthesiology*. 1985;62(4):396-405. Copyright © 1985 American Society of Anesthesiologists, Inc.

Tachycardia can enhance frequency-dependent blockade of cardiac sodium channels by bupivacaine, further contributing to the selective cardiac toxicity of this local anesthetic.⁷⁶ Conversely, a low degree of frequency-dependent blockade may contribute to the antidysrhythmic properties of lidocaine. In anesthetized dogs, bretylium, 20 mg/kg IV, reverses bupivacaine-induced cardiac depression and increases the threshold for ventricular tachycardia.⁷⁷ In an effort to decrease the potential for cardiotoxicity should accidental intravascular injection occur, it may be prudent to limit the concentration of bupivacaine to be used for epidural anesthesia to 0.5%. In addition, slow or fractionated administration of all local anesthetics, but

particularly bupivacaine, to detect systemic toxicity from accidental intravascular injection, should help decrease the risk of cardiotoxicity.⁷⁸

Treatment of Local Anesthetic Systemic Toxicity

Treatment of LAST has undergone swift changes in last decade and includes prompt airway management, circulatory support, and mechanisms to remove local anesthetic from the receptor sites. Treatment should be instituted at earliest suspicion of toxicity. Treatment of local anesthetic-induced seizures includes ventilation of the patient's lungs with oxygen because arterial hypoxemia and metabolic acidosis occur within seconds.⁷⁹ The IV administration of a benzodiazepine such as midazolam or diazepam is effective in suppressing local anesthetic-induced seizures. Propofol can be used for seizures treatment if hemodynamic stability is confirmed. For persistent seizures patient should be paralyzed using succinylcholine or nondepolarizing blockers, to prevent prevent acidosis and hypoxia. Early use of lipid emulsion for the treatment of local anesthetic toxicity is becoming standard of care. Multiple published cases have shown that intralipid can be successfully used for resuscitation; the mean total (bolus plus infusion) intralipid dose over the first 30 minutes was 3.8 mL/kg (range, 1.2–6.0 mL/kg). American Society of Regional Anesthesia and Pain Medicine has published specific recommendations and a checklist for treatment of LAST (**Figure 10.11**).^{51,80,81} Use of lipid emulsion is recommended at earliest sign of toxicity after airway management. An initial bolus of 1.5 mL/kg 20% lipid emulsion followed by 0.25 mL/kg per minute of infusion continued for at least 10 minutes after circulatory stability is attained is recommended. Epinephrine should be used at lower dose, 10 to 100 µg, and vasopressin use is not recommended. Calcium channel blockers and β blockers should be avoided. Nonresponse to treatment should prompt institution of cardiopulmonary bypass.

- A. If signs and symptoms of LAST occur, prompt and effective airway management is crucial to preventing hypoxia and acidosis, which are known to potentiate LAST.
- B. If seizures occur, they should be rapidly halted with benzodiazepines. If benzodiazepines are not readily available, small doses of propofol or thiopental are acceptable.
- C. Although propofol can stop seizures, large doses further depress cardiac function; propofol should be avoided when there are signs of CV compromise. If seizures persist despite benzodiazepines, small doses of succinylcholine or similar neuromuscular blocker should be considered to minimize acidosis and hypoxemia.
- D. If cardiac arrest occurs, we recommend standard Advanced Cardiac Life Support with the following modifications:
 - If epinephrine is used, small initial doses (10–100 µg boluses in the adult) are preferred.
 - Vasopressin is not recommended.
 - Avoid calcium channel blockers and β-adrenergic receptor blockers.
 - If ventricular arrhythmias develop, amiodarone is preferred.
- E. Lipid emulsion therapy
 - Consider administering at the first signs of LAST, after airway management.
 - Dosing:
 - 1.5 mL/kg 20% lipid emulsion bolus
 - 0.25 mL/kg per minute of infusion, continued for at least 10 minutes after circulatory stability is attained
 - If circulatory stability is not attained, consider rebolus and increasing infusion to 0.5 mL/kg per minute.
 - Approximately 10 mL/kg lipid emulsion for 30 minutes is recommended as the upper limit for initial dosing
- F. Propofol is not a substitute for lipid emulsion.
- G. Failure to respond to lipid emulsion and vasopressor therapy should prompt institution of cardiopulmonary bypass (CPB). Because there can be considerable lag in beginning CPB, it is reasonable to notify the closest facility capable of providing it when CV compromise is first identified during an episode of LAST.

FIGURE 10.11 American Society of Regional Anesthesia and Pain Medicine recommendations for managing local anesthetic systemic toxicity (LAST). CV, cardiovascular. *From Neal JM, Bernards CM, Butterworth JF IV, et al. ASRA practice advisory on local anesthetic systemic toxicity. Reg Anesth Pain Med. 2010;35:152–161.*

Neural Tissue Toxicity (Neurotoxicity)

Neurotoxicity from placement of local anesthetic-containing solutions into the epidural or subarachnoid space can lead various complications. The spectrum of this neurotoxicity may range from patchy groin numbness and persistent isolated myotomal weakness to cauda equina syndrome.⁸² Myofascial pain may be erroneously diagnosed as transient neurologic symptoms after intrathecal placement of local anesthetics.⁸³ Overall,

permanent neurologic injury after regional anesthesia remains a very rare event.^{84,85} Lidocaine-induced increases in intracellular calcium ion concentrations may be the mechanism for this toxicity.⁸⁶

Transient Neurologic Symptoms

Transient neurologic symptoms manifest as moderate to severe pain in the lower back, buttocks, and posterior thighs that appears within 6 to 36 hours after complete recovery from uneventful single-shot spinal anesthesia.⁸⁷ The etiology of transient neurologic symptoms is not known, but relief of pain with trigger point injections and nonsteroidal antiinflammatory drugs suggests a musculoskeletal component. In transient neurologic symptoms, the sensory and motor neurologic examination is not abnormal and full recovery from symptoms usually occurs within 1 to 7 days.

The incidence of transient neurologic symptoms is greatest following the intrathecal injection of lidocaine (as high as 30%).⁸⁸ Initial reports of transient neurologic symptoms involved spinal anesthesia produced by hyperbaric 5% lidocaine, suggesting that the observed neurotoxicity might be, at least in part, concentration dependent. Nevertheless, the incidence of transient neurologic symptoms is similar after intrathecal placement of 1 mg/kg of either 5% or 2% lidocaine in 7.5% glucose.^{89,90} For ambulatory patients undergoing arthroscopy, the incidence of transient neurologic symptoms is not altered by decreasing spinal lidocaine concentrations from 2% to 1% or 0.5% and are similar to the incidence of symptoms described with 5% lidocaine.⁹¹ The risk of transient neurologic symptoms associated with bupivacaine, tetracaine, mepivacaine, prilocaine, or procaine is significantly less than with lidocaine.⁹² In a recent Cochrane review, spinal anesthesia with lidocaine was associated with significantly higher incidence of transient neurologic symptoms when compared to bupivacaine, prilocaine, or procaine.⁹³

Lithotomy position,⁹⁴ early ambulation,⁹⁵ the glucose concentration, and osmolarity of the anesthetic solution do not influence the incidence of transient neurologic symptoms.⁹⁴ Vasoconstrictors can decrease blood supply to the nerve, and there is evidence that adding phenylephrine to the local anesthetic solution increases the incidence of transient neurologic symptoms after spinal anesthesia with tetracaine.⁹⁴ There are some clinical data suggesting that addition of epinephrine to local anesthetic solutions does not alter the incidence of transient neurologic symptoms.⁹⁶

Cauda Equina Syndrome

Cauda equina syndrome occurs when diffuse injury across the lumbosacral plexus produces varying degrees of sensory anesthesia, bowel and bladder sphincter dysfunction, and paraplegia. Cauda equina syndrome is most frequently associated with large central lumbar disc herniation, prolapse, or sequestration with 50% to 60% patients having urinary retention on presentation.⁹⁷ In the regional anesthesia literature, initial reports of cauda equina syndrome were associated with the use of hyperbaric 5% lidocaine for continuous spinal anesthesia.^{98,99} In these cases, it was postulated that microcatheters used during continuous spinal anesthesia (28 gauge or smaller) contributed to nonhomogeneous distribution of the local anesthetic solution, with pooling of high concentrations of the local anesthetic solution on certain dependent or stretched (lithotomy position) nerves. Nevertheless, this same complication has also been reported after intrathecal injection of 100 mg of 5% lidocaine through a 25-gauge needle.¹⁰⁰

Anterior Spinal Artery Syndrome

Anterior spinal artery syndrome consists of lower extremity paresis with a variable sensory deficit that is usually diagnosed as the neuraxial blockade fails to resolve. The etiology of this syndrome is uncertain, although thrombosis or spasm of the anterior spinal artery is possible as well as effects of hypotension or vasoconstrictor drugs. Although the addition of epinephrine to local anesthetic solutions has been implicated as a theoretical cause, spinal cord perfusion studies do not show a deleterious effect of the catecholamine.¹⁰¹ Advanced age and the presence of peripheral vascular disease may predispose patients to development of anterior spinal artery syndrome. It may be difficult to distinguish symptoms due to anterior spinal artery syndrome from those caused by spinal cord compression produced by an epidural abscess or hematoma.

Methemoglobinemia

Methemoglobinemia is a rare but potentially life-threatening complication (decreased oxygen-carrying capacity) that may follow the administration of certain drugs or chemicals that cause oxidation of hemoglobin to methemoglobin more rapidly than methemoglobin is reduced to hemoglobin. Known oxidant substances include topical local anesthetics (prilocaine, benzocaine, cetacaine, lidocaine), nitroglycerin, phenytoin, and sulfonamides.¹⁰² Neonates may be at greater risk because of more readily oxidized fetal hemoglobin.

Methemoglobin cannot bind oxygen or carbon dioxide, resulting in loss of the hemoglobin molecule's transport function. Methemoglobin normally constitutes <1% of the total hemoglobin. Central cyanosis usually occurs when methemoglobin concentrations exceed 15%. The presence of methemoglobinemia is suggested by a difference between the calculated and measured arterial oxygen saturation. The diagnosis is confirmed by qualitative measurements of methemoglobin by co-oximetry.

Methemoglobinemia is readily reversed by the administration of methylene blue, 1 to 2 mg/kg IV, over 5 minutes (total dose should not exceed 7-8 mg/kg). Methylene blue is reduced to leukomethylene blue, which then acts as an electron donor and nonenzymatically reduces methemoglobin to hemoglobin. Normal levels of methemoglobin should be achieved within 20 to 60 minutes after the administration of methylene blue. This therapeutic effect, however, is short lived because methylene blue may be cleared before conversion of all the methemoglobin to hemoglobin. Furthermore, continued absorption of highly lipophilic local anesthetics such as benzocaine from adipose tissue stores may continue to occur after methylene blue plasma concentrations are no longer therapeutic.

Ventilatory Response to Hypoxia

Lidocaine at clinically useful plasma concentrations depresses the ventilatory responses to arterial hypoxemia.¹⁰³ In this regard, patients with carbon dioxide retention whose resting ventilation depends on hypoxic drive may be at risk of ventilatory failure when lidocaine is administered for treatment of cardiac dysrhythmias. Conversely, systemic absorption of bupivacaine, such as follows a brachial plexus block, stimulates the ventilatory response to carbon dioxide.

Hepatotoxicity

Continuous or intermittent epidural administration of bupivacaine to treat postherpetic neuralgia has been associated with increased plasma concentrations of liver transaminase enzymes that normalized when bupivacaine infusion was discontinued or lidocaine was substituted for bupivacaine.¹⁰⁴ The preservative present in both local anesthetics was the same. Drug-induced liver injury can be a direct toxic injury, an allergic reaction, or an idiosyncratic metabolic abnormality. The hepatic dysfunction described seems most likely to represent an allergic reaction.¹⁰⁵

Uses of Local Anesthetics

Local anesthetics are most often used to produce topical, infiltration, and regional anesthesia.^{52,106} Less common reasons to select local anesthetics are to prevent or treat cardiac dysrhythmias, prevent or treat increases in intracranial pressure, provide analgesia, and treat grand mal seizures. Antiinflammatory effects of local anesthetics may be responsible for beneficial effects in the perioperative period that are attributed to spinal or epidural anesthesia.¹⁰⁷

Regional Anesthesia

Regional anesthesia is classified according to the following six sites of placement of the local anesthetic solution: (1) topical or surface anesthesia, (2) local infiltration, (3) peripheral nerve block, (4) IV regional anesthesia (Bier block), (5) epidural anesthesia, and (6) spinal (subarachnoid) anesthesia (**Table 10.3**). Maximum doses of local anesthetics (based on body weight) as recommended for topical or peripheral nerve block anesthesia must be viewed as imprecise guidelines that often do not consider the pharmacokinetics of the drugs.²

TABLE 10.3

Clinical uses of local anesthetics

	Clinical use	Concentration (%)	Onset	Duration (minutes)	Recommended maximum single dose (mg)
Lidocaine	Topical	4	Fast	30-60	300
	Infiltration	0.5-1	Fast	60-240	300 or 500 with epinephrine
	IVRA	0.25-0.5	Fast	30-60	300
	PNB	1-1.5	Fast	60-180	300 or 500 with epinephrine
	Epidural	1.5-2	Fast	60-120	300 or 500 with epinephrine
	Spinal	1.5-5	Fast	30-60	100
Mepivacaine	Infiltration	0.5-1	Fast	60-240	400 or 500 with epinephrine
	PNB	1-1.5	Fast	120-240	400 or 500 with epinephrine
	Epidural	1.5-2	Fast	60-180	400 or 500 with epinephrine
	Spinal	2-4	Fast	60-120	100
Prilocaine	Infiltration	0.5-1	Fast	60-120	600
	IVRA	0.25-0.5	Fast	30-60	600
	PNB	1.5-2	Fast	90-180	600
	Epidural	2-3	Fast	60-180	600
Bupivacaine	Infiltration	0.25	Fast	120-480	175 or 225 with epinephrine
	PNB	0.25-0.5	Slow	240-960	175 or 225 with epinephrine
	Epidural	0.5-0.75	Moderate	120-300	175 or 225 with epinephrine
	Spinal	0.5-0.75	Fast	60-240	20
Levobupivacaine	Infiltration	0.25	Fast	120-480	150
	PNB	0.25-0.5	Slow	840-1,020	150
	Epidural	0.5-0.75	Moderate	300-540	150
	Spinal	0.5-0.75	Fast	60-360	20
Ropivacaine	Infiltration	0.2-0.5	Fast	120-360	200
	PNB	0.5-1	Slow	300-480	250
	Epidural	0.5-1	Moderate	120-360	200
Chloroprocaine	Infiltration	1	Fast	30-60	800 or 1,000 with epinephrine
	PNB	2	Fast	30-60	800 or 1,000 with epinephrine
	Epidural	2-3	Fast	30-60	800 or 1,000 with epinephrine
	Spinal	2-3	Fast	30-60	Preservative free ^a
Procaine	Spinal	10	Fast	30-60	1,000
Tetracaine	Topical	2	Fast	30-60	20
	Spinal	0.5	Fast	120-360	20
Benzocaine	Topical	Up to 20%	Fast	30-60	200
Cocaine	Topical	4-10	Fast	30-60	150

Abbreviations: IVRA, intravenous regional anesthesia; PNB, peripheral nerve block.

^aOff-label use.

Adapted from Covino BG, Wildsmith JAW. Clinical pharmacology of local anesthetic agents. In: Cousins MJ, Bridenbaugh PO, eds. *Neural Blockade in Clinical Anesthesia and Management of Pain*. Philadelphia, PA: Lippincott-Raven; 1998:97-128 and Foster RH, Markham A. Levobupivacaine: a review of its pharmacology and use as a local anesthetic. *Drugs*. 2000;59:551-559.

Topical Anesthesia

Local anesthetics are used to produce topical anesthesia by placement on the mucous membranes of the nose, mouth, tracheobronchial tree, esophagus, or genitourinary tract. Cocaine (4%-10%), tetracaine (1%-2%), and lidocaine (2%-4%) are most often used. Cocaine's popularity for topical anesthesia reflects its unique ability to produce localized vasoconstriction, thus decreasing blood loss and improving surgical visualization (see "[Cocaine Toxicity](#)" section). There is no difference between the intranasal anesthetic or vasoconstrictive effects of cocaine and those of a lidocaine-oxymetazoline or tetracaine-oxymetazoline mixture, emphasizing the usefulness of these combinations as substitutes for cocaine.¹⁰⁸ Procaine and chloroprocaine penetrate mucous membranes poorly and are ineffective for topical anesthesia.

Nebulized lidocaine is used to produce surface anesthesia of the upper and lower respiratory tract before fiberoptic laryngoscopy and/or bronchoscopy and as a treatment for patients experiencing intractable coughing.¹⁰⁹ The inhalation of local anesthetics by normal subjects does not alter airway resistance and may even produce mild bronchodilation.¹¹⁰ In contrast, inhalation of nebulized lidocaine can cause bronchoconstriction in some patients with asthma, which may become an important consideration when bronchoscopy is planned in these patients.¹⁰⁹ Local anesthetics are absorbed into the systemic circulation after topical application to mucous membranes. Systemic absorption of tetracaine, and to a lesser extent lidocaine, after placement on the tracheobronchial mucosa produces plasma concentrations similar to those present after IV injection of the local anesthetic. For example, plasma lidocaine concentrations 15 minutes after laryngotracheal spray of the local anesthetic are similar to those concentrations present at the same time after an IV injection of lidocaine.¹¹¹ This systemic absorption reflects the high vascularity of the tracheobronchial tree and the injection of the local anesthetic as a spray that spreads the solution over a wide surface area.

Eutectic Mixture of Local Anesthetics

The keratinized layer of the skin provides an effective barrier to diffusion of topical drugs, making it difficult to achieve anesthesia of intact skin by topical application. A popular use of prilocaine is for topical anesthesia when used in an eutectic mixture. A 5% lidocaine-prilocaine cream (2.5% lidocaine and 2.5% prilocaine) allows the use of high concentrations of the anesthetic bases without concern about local irritation, uneven absorption, or systemic toxicity.^{112,113} This combination of local anesthetics is considered a eutectic mixture of local anesthetics (EMLA), as the melting point of the combined drugs is lower than lidocaine or prilocaine alone. The EMLA cream acts by diffusing through intact skin to block neuronal transmission from dermal receptors. Usually, 1 to 2 g of EMLA cream are applied per a 10-cm² area of skin and covered with an occlusive dressing. The duration of application varies according to the type of procedure being undertaken and the site of application. For example, skin-graft harvesting requires 2 hours, whereas cautery of genital warts can be undertaken after only a 10-minute application. The EMLA cream is effective in relieving the pain of venipuncture, arterial cannulation, lumbar puncture, and myringotomy in children and adults. Pain during circumcision in neonates is attenuated by this topical anesthetic.¹¹³ Although 45 minutes have been suggested as the minimum effective onset time for decreasing the pain of IV cannulation, a significant decrease in pain scores may be noted after only 5 minutes. Low-frequency ultrasound pretreatment is effective in accelerating the onset of EMLA cream.¹¹⁴ The addition of nitroglycerin ointment to EMLA cream increases the ease of venous cannulation by promoting venodilation.¹¹⁵ If EMLA cream is used to anesthetize the skin before blood sampling, the results of the analyses of the blood are not distorted. However, the use of EMLA cream to prevent the pain of intradermal skin tests decreases the flare response and may lead to false-negative interpretation of weakly positive tests.

Skin blood flow, epidermal and dermal thickness, duration of application, and the presence of skin pathology are important factors affecting the onset, efficacy, and duration of EMLA analgesia. African Americans may be less responsive than whites, presumably because of increased density of the stratum corneum.¹¹⁶ Blanching of the skin may be seen after 30 to 60 minutes, probably due to vasoconstriction. Plasma levels of lidocaine and prilocaine are below toxic levels, although methemoglobin concentrations reflecting the metabolism of prilocaine may be increased in children younger than 3 months of age, reflecting immature reductase pathways. The enzyme capacity for red blood cell methemoglobin reductase in children

younger than 3 months of age can be overloaded when EMLA cream is administered concurrently with other methemoglobin-inducing drugs (sulfonamides, acetaminophen, phenytoin, nitroglycerin, nitroprusside).¹¹⁷ Likewise, EMLA cream should not be used in those rare patients with congenital or idiopathic methemoglobinemia. Local skin reactions, such as pallor, erythema, and alterations in temperature sensation; edema; pruritus; and rash are common after EMLA cream application.

The EMLA cream is not recommended for use on mucous membranes because of the faster absorption of lidocaine and prilocaine than through intact skin.¹¹² Similarly, EMLA cream is not recommended for skin wounds, and the risk of wound infection may be increased.¹¹⁸ Patients being treated with certain antidysrhythmic drugs (mexiletine) may experience additive and potentially synergistic effects when exposed to EMLA cream. The EMLA cream is contraindicated in patients with a known history of allergy to amide local anesthetics.

Other Topically Effective Local Anesthetics

Amethocaine, like EMLA cream, requires several minutes to become effective, and the cream must be covered with an occlusive dressing. A microemulsion of amethocaine increases skin penetration and shortens the time until cutaneous anesthesia is achieved.¹¹⁹ New commercial preparations for topical anesthesia are being developed. Ametop gel (4% tetracaine) is used to provide topical anesthesia for venous cannulation, and Rapydan patch (7% lidocaine and 7% tetracaine) has been developed to provide topical anesthesia by a different mechanism (heat assisted delivery). They provide comparable pain relief for venous cannulation in 90% of the patients.¹²⁰

Local Infiltration

Local infiltration anesthesia involves extravascular placement of local anesthetic in the area to be anesthetized. Subcutaneous injection of the local anesthetic in the area to be traversed for placement of an intravascular cannula is one example. Lidocaine is the local anesthetic most often selected for infiltration anesthesia. Infiltration of 0.25% ropivacaine or bupivacaine is equally effective in the management of pain at an inguinal operative site.¹²¹

The duration of infiltration anesthesia can be approximately doubled by adding 1:200,000 epinephrine to the local anesthetic solution. Epinephrine-containing solutions, however, should not be injected intracutaneously or into tissues supplied by end arteries (fingers, ears, and nose) because resulting vasoconstriction can produce ischemia and even gangrene.

Peripheral Nerve Block Anesthesia

Peripheral nerve block anesthesia is achieved by injection of local anesthetic solutions into tissues surrounding individual peripheral nerves or nerve plexuses such as the brachial plexus. When local anesthetic solutions are deposited in the vicinity of a peripheral nerve, they diffuse from the outer surface (mantle) toward the center (core) of the nerve along a concentration gradient.¹²² Consequently, nerve fibers located in the mantle of the mixed nerve are anesthetized first. These mantle fibers usually are distributed to more proximal anatomic structures in contrast to distal structures innervated by nerve fibers near the core of the nerve. This explains the initial development of anesthesia proximally, with subsequent distal spread as local anesthetic solution diffuses to reach more central core nerve fibers. Conversely, recovery of sensation occurs in a reverse direction; nerve fibers in the mantle that are exposed to extraneural fluid are the first to lose local anesthetic so that sensation returns initially to the proximal and last to the distal parts of the limb.

Skeletal muscle paralysis may precede the onset of sensory anesthesia if motor nerve fibers are distributed peripheral to sensory fibers in the mixed peripheral nerve.^{122,123} Indeed, the sequence of onset and recovery from blockade of sympathetic, sensory, and motor nerve fibers in a mixed peripheral nerve depends as much on anatomic location of the nerve fibers within the mixed nerve as on their sensitivity to local anesthetics. This differs from results of in vitro studies on single nerve fibers, in which diffusion distance does not play a role. In an in vitro model, nerve fiber size is most important, with the onset of conduction blockade being inversely proportional to fiber size. For example, the smallest sensory and autonomic nervous system fibers are anesthetized first, followed by larger motor and proprioceptive axons.

The rapidity of onset of sensory anesthesia after injection of a local anesthetic solution into tissues around a peripheral nerve depends on the pK of the drug. The pK determines the amount of local anesthetic that exists in the active nonionized form at the pH of the tissue (see [Table 10.1](#)). For example, the onset of action of lidocaine occurs in approximately 3 minutes, whereas onset after injection of bupivacaine, levobupivacaine, or ropivacaine requires approximately 15 minutes, reflecting the greater fraction of lidocaine that exists in the lipid-soluble nonionized form. The onset and duration of sensory anesthesia for brachial plexus block produced by 0.5% bupivacaine, levobupivacaine, or ropivacaine is similar. Tetracaine, with a slow onset of anesthesia and a high potential to cause systemic toxicity, is not recommended for local infiltration or peripheral nerve block anesthesia.

Duration of peripheral nerve block anesthesia depends on the dose of local anesthetic, its lipid solubility, its degree of protein binding, and concomitant use of a vasoconstrictor such as epinephrine. The duration of action is prolonged more safely by epinephrine than by increasing the dose of local anesthetic, which also increases the likelihood of systemic toxicity. Conversely, not all reports document a prolongation of the duration of action when epinephrine is added to bupivacaine or ropivacaine.^{[124](#)}

Continuous Peripheral Nerve Blocks

Modern regional anesthesia practice has moved toward ultrasound-guided peripheral nerve blocks and using catheter for continuous infusions. Use of ultrasound guidance increases the chances for successful block, takes less time to perform, hasten onset, and is longer duration when compared to those performed with peripheral nerve stimulation guidance.^{[125](#)} Ultrasound guidance also decreased the risk of vascular puncture during block performance. This provides more consistent nerve block and also analgesia for few days after the surgery, depending on type of local anesthetic medication used. Continuous nerve blocks have shown to be associated with improved pain control, decreased need for opioid analgesics, less nausea, and greater patient satisfaction, when compared to single shot blocks.^{[126](#)} Commonly used medication and dosages are shown in [Table 10.4](#). Midazolam, magnesium, dexmedetomidine, and ketamine have been used as additives to local anesthetic solutions for peripheral nerve blocks, but they cannot be routinely recommended due to a dearth of supportive data, modest efficacy, and (in the case of ketamine) significant adverse effects.^{[127](#)}

TABLE 10.4

Dosage chart for common continuous nerve blocks

Block type	Local anesthetic	Continuous rate (mL per hour)	Bolus dose (mL)	Lock out interval (minutes)	Number of doses per hour
Interscalene	0.25% bupivacaine or 0.2% ropivacaine	8	12	60	1
Supraclavicular	0.25% bupivacaine or 0.2% ropivacaine	8	12	60	1
Popliteal	0.25% bupivacaine or 0.2% ropivacaine	8	12	60	1
Femoral ^a	0.12% bupivacaine or 0.1% ropivacaine	8	0

^aLower concentration used for femoral block to reduce the chances of motor blockade and to prevent falls.

Intravenous Regional Anesthesia (Bier Block)

The IV injection of a local anesthetic solution into an extremity isolated from the rest of the systemic circulation by a tourniquet produces a rapid onset of anesthesia and skeletal muscle relaxation. The duration of anesthesia is independent of the specific local anesthetic and is determined by how long the tourniquet is kept inflated. The mechanism by which local anesthetics produce IV regional anesthesia is unknown but probably reflects action of the drug on nerve endings as well as nerve trunks. Normal sensation and skeletal

muscle tone return promptly on release of the tourniquet, which allows blood flow to dilute the concentration of local anesthetic.

Ester and amide local anesthetics produce satisfactory effects when used for IV regional anesthesia. Lidocaine is the most frequently selected amide local anesthetic for producing this type of regional anesthesia. Alternatives to lidocaine include prilocaine, mepivacaine, and ropivacaine. The onset, duration, and quality of IV regional anesthesia produced by 50 mL of a 0.5% solution of lidocaine or prilocaine are similar, but plasma concentrations of prilocaine are lower than those of lidocaine after tourniquet deflation ([Figure 10.12](#)).¹²⁸ The associated degree of methemoglobinemia (3% of hemoglobin as methemoglobin) seen with prilocaine is far below the level needed to produce cyanosis (10% hemoglobin as methemoglobin). The significantly lower plasma prilocaine concentrations after tourniquet deflation may indicate a greater margin of safety for prilocaine compared to lidocaine in terms of potential systemic toxicity. Mepivacaine 5 mg/kg provided superior analgesia to lidocaine 3 mg/kg when used for IV regional anesthesia.¹²⁹ Plasma concentrations of lidocaine decreased significantly in the first 60 minutes following tourniquet deflation, whereas blood concentrations of mepivacaine remained below toxic concentrations. Ropivacaine, 1.2 and 1.8 mg/kg, compared with lidocaine, 3 mg/kg, produced comparable IV regional anesthesia, but residual analgesia was longer lasting with ropivacaine.¹³⁰ Chloroprocaine is not selected for IV regional anesthesia because of a high incidence of thrombophlebitis. Bupivacaine is not recommended for IV regional anesthesia considering its greater likelihood than other local anesthetics for producing cardiotoxicity when the tourniquet is deflated at the conclusion of the anesthetic. Ropivacaine, although less likely to produce cardiotoxicity than bupivacaine, is not recommended for IV regional anesthesia.

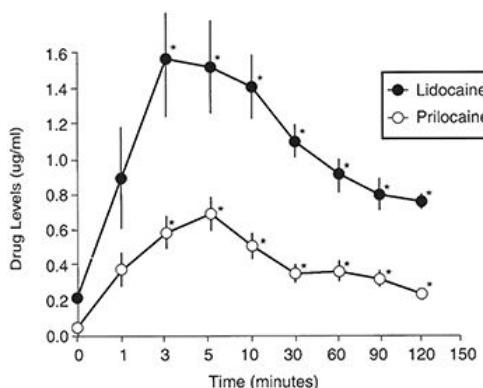


FIGURE 10.12 After tourniquet deflation, plasma concentrations of lidocaine exceed concentrations of prilocaine (mean \pm standard error; $*P < .05$). Reprinted with permission from Bader AM, Concepcion M, Hurley RJ, et al. Comparison of lidocaine and prilocaine for intravenous regional anesthesia. Anesthesiology. 1988;69(3):409-412. Copyright © 1988 American Society of Anesthesiologists, Inc.

Epidural Anesthesia

Local anesthetic solutions placed in the epidural or sacral caudal space produce epidural anesthesia by two presumed mechanisms. First, local anesthetic diffuses across the dura to act on nerve roots and the spinal cord as it does when injected directly into the lumbar subarachnoid space to produce spinal anesthesia. Second, local anesthetic also diffuses into the paravertebral area through the intervertebral foramina, producing multiple paravertebral nerve blocks. These slow diffusion processes account for the 15- to 30-minute delay in onset of sensory anesthesia after placement of local anesthetic solutions in the epidural space. Lidocaine is commonly used for epidural anesthesia because of its good diffusion capabilities through tissues. Despite a reasonable safety profile of bupivacaine, many clinicians prefer to use the costly ropivacaine or levobupivacaine because ropivacaine or levobupivacaine are associated with less risk for cardiac and CNS toxicity and are also less likely to result in unwanted postoperative motor blockade.¹³¹ The delivery of local anesthetic in epidural space is achieved mostly by a continuous epidural infusion with an option of patient-

controlled epidural bolus option. For labor analgesia, novel programmed intermittent bolus is superior to continuous epidural infusion.¹³²

Bupivacaine and ropivacaine at similar concentrations (0.5% to 0.75%) produce similar prolonged sensory anesthesia (ropivacaine has a greater tendency to block A- δ and C fibers) when used for epidural anesthesia, but the motor anesthesia produced by ropivacaine is less intense and of shorter duration.^{133,134} These characteristics of ropivacaine may be advantageous for obstetric patients in labor and for those experiencing acute and chronic pain. The addition of epinephrine 1:200,000 to 0.5% or 0.75% bupivacaine or ropivacaine does not appear to offer an advantage in terms of duration of action.¹³⁵ Use of 1% ropivacaine may provide longer sensory anesthesia than 0.75% bupivacaine, whereas the motor block is similar.^{124,136} The lower systemic toxicity of ropivacaine compared with bupivacaine enables ropivacaine to be used for surgical anesthesia in concentrations up to 1%.⁵ For postoperative analgesia, the infusion of 0.2% ropivacaine at 6 to 10 mL per hour is effective.¹³⁷

In children, there is no difference with regard to postoperative analgesia provided by bupivacaine, levobupivacaine, or ropivacaine, but unwanted motor blockade was more frequent in patients receiving bupivacaine (**Figure 10.13**).¹³⁸

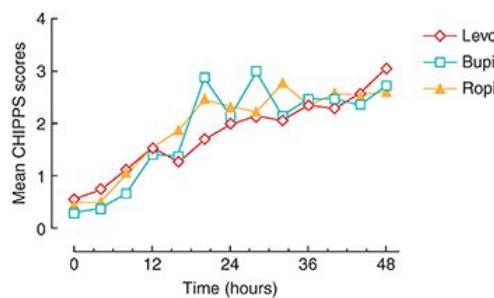


FIGURE 10.13 Mean postoperative pain scores (Children's and Infant's Postoperative Pain Score [CHIPPS]) were similar in patients receiving epidural levobupivacaine (levo), bupivacaine (bupi), and ropivacaine (ropi) infusions. Reprinted with permission from De Negri P, Ivani G, Tirri T, et al. A comparison of epidural bupivacaine, levobupivacaine, and ropivacaine on postoperative analgesia and motor blockade. Anesth Analg. 2004;99(1):45-48. Copyright © 2004 International Anesthesia Research Society.

In contrast to spinal anesthesia, during epidural anesthesia, there often is not a zone of differential sympathetic nervous system blockade, and the zone of differential motor blockade may average up to four rather than two segments below the sensory level. Another difference from spinal anesthesia is the larger dose required to produce epidural anesthesia, leading to substantial systemic absorption of the local anesthetic. For example, peak plasma concentrations of lidocaine are 3 to 4 μ g/mL after placement of 400 mg into the epidural space. Bupivacaine, 70 to 100 mg of 0.5% with 1:200,000 epinephrine placed in the epidural space, results in peak average plasma concentrations of 0.335 μ g/mL occurring about 30 minutes after instillation of the local anesthetic.¹³⁹ Peak plasma concentrations of bupivacaine near 1 μ g/mL occur when epinephrine is not added to the local anesthetic solution placed in the epidural space. In this regard, addition of epinephrine to the local anesthetic solution may decrease systemic absorption of the local anesthetic by approximately one-third. The peak venous plasma concentration of ropivacaine is 1.3 μ g/mL after epidural placement of 200 mg of the local anesthetic. Addition of 1:200,000 epinephrine solution decreases systemic absorption of ropivacaine by approximately one-third. Systemic absorption of epinephrine produces β -adrenergic stimulation characterized by peripheral vasodilation, with resultant decreases in systemic blood pressure, even though the inotropic and chronotropic effects of epinephrine increase cardiac output.

Addition of opioids to local anesthetic solutions placed in the epidural or intrathecal space results in synergistic analgesia.¹⁴⁰ An exception to this analgesic synergy is 2-chloroprocaine, which appears to decrease the effectiveness of epidural opioids when administered with local anesthetic solutions placed into the epidural space.¹⁴¹ Combining local anesthetics and opioids for peripheral nerve blocks appears to be ineffective in altering the characteristics or results of the block.

Spinal Anesthesia

Spinal anesthesia is produced by injection of local anesthetic solutions into the lumbar subarachnoid space. Local anesthetic solutions placed into lumbar cerebrospinal fluid act on superficial layers of the spinal cord, but the principal site of action is the preganglionic fibers as they leave the spinal cord in the anterior rami. Because the concentration of local anesthetics in cerebrospinal fluid decreases as a function of distance from the site of injection, and because different types of nerve fibers differ in their sensitivity to the effects of local anesthetics, zones of differential anesthesia develop. Because preganglionic sympathetic nervous system fibers are blocked by concentrations of local anesthetics that are insufficient to affect sensory or motor fibers, the level of sympathetic nervous system denervation during spinal anesthesia extends approximately two spinal segments cephalad to the level of sensory anesthesia. For the same reasons, the level of motor anesthesia averages two segments below sensory anesthesia.

Dosages of local anesthetics used for spinal anesthesia vary according to the (1) height of the patient, which determines the volume of the subarachnoid space; (2) segmental level of anesthesia desired; and (3) duration of anesthesia desired. The total dose of local anesthetic administered for spinal anesthesia is more important than the concentration of drug or the volume of the solution injected.

Spinal anesthesia with lidocaine has been reported to produce a higher incidence of transient neurologic symptoms than spinal anesthesia produced by bupivacaine (see “[Neural Tissue Toxicity \[Neurotoxicity\]](#)” section). For these reasons, bupivacaine has been proposed as an alternative local anesthetic to lidocaine for spinal anesthesia.^{142,143} If lidocaine is selected, it may be prudent to limit the dose to 60 mg.¹⁴³ Bupivacaine used for spinal anesthesia is more effective than tetracaine in preventing lower extremity tourniquet pain during orthopedic surgery.¹⁴⁴ This effectiveness may reflect the ability of bupivacaine to produce greater frequency-dependent conduction blockade of fibers than does tetracaine. In parturients, the intrathecal placement of bupivacaine, 2.5 mg, plus sufentanil, 10 µg, provided labor analgesia and allowed the patients to continue to ambulate.¹⁴⁵ The addition of intrathecal fentanyl 5 µg provides a bupivacaine dose-sparing effect similar to that provided by 15 or 25 µg of fentanyl, resulting in less pruritus but a shortening of the duration of action.¹⁴⁶

Ropivacaine, 3 mL of 0.5% or 0.75%, produces sensory anesthesia, although complete motor blockade was present in only about 50% of patients receiving the lower dose.¹⁴⁷ Ropivacaine is an acceptable local anesthetic to produce spinal anesthesia for cesarean section, and decreased lower extremity blockade compared with bupivacaine may be a desirable feature.^{148,149} Levobupivacaine has equivalent clinical efficacy to bupivacaine for spinal anesthesia ([Figure 10.14](#)).¹⁵⁰ Dibucaine is 1.5 to 2.0 times as potent as tetracaine when used for spinal anesthesia. In the past, chloroprocaine was not recommended for placement in the subarachnoid space because of potential neurotoxicity.^{151–153} However, preservative-free 2-chloroprocaine solutions (2% and 3%) are available for intrathecal injection and have been shown to produce reliable sensory and motor blockade with a short duration and little or no risk of transient neurologic symptoms, making this local anesthetic an attractive selection for outpatient surgical procedures performed under spinal anesthesia ([Figure 10.15](#)).^{154–156}

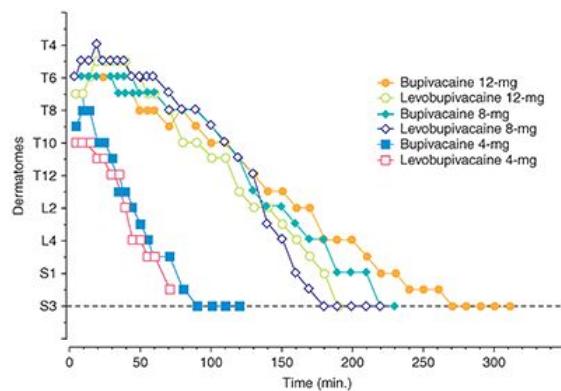


FIGURE 10.14 Recovery from sensory block occurs at a similar rate following spinal anesthesia produced with equipotent doses of bupivacaine and levobupivacaine. Reprinted with permission from Alley EA, Kopacz DJ, McDonald SB, et al. Hyperbaric spinal levobupivacaine: A comparison to racemic bupivacaine in volunteers. Anesth Analg. 2002;94(1):188-193. Copyright © 2002 International Anesthesia Research Society.

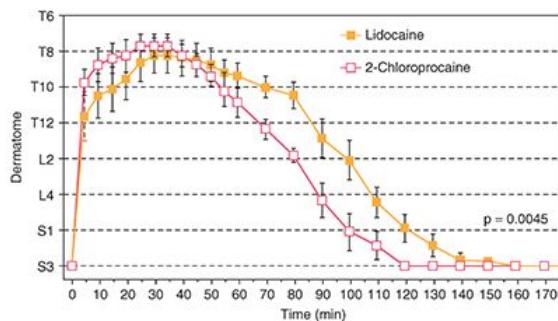


FIGURE 10.15 Recovery of sensory block is more rapid following spinal anesthesia produced with 2-chloroprocaine than with lidocaine. Reprinted with permission from Kouri ME, Kopacz DJ. Spinal 2-chloroprocaine: a comparison with lidocaine in volunteers. Anesth Analg. 2004;98(1):75-80. Copyright © 2004 International Anesthesia Research Society.

The specific gravity of local anesthetic solutions injected into the lumbar cerebrospinal fluid is important in determining spread of the drugs. Addition of glucose to local anesthetic solutions increases the specific gravity of local anesthetic solutions above that of cerebrospinal fluid (hyperbaric). Addition of distilled water lowers the specific gravity of local anesthetic solutions below that of cerebrospinal fluid (hypobaric). Cerebrospinal fluid does not contain significant amounts of cholinesterase enzyme; therefore, the duration of action of ester local anesthetics as well as amides placed in the subarachnoid space depends on systemic absorption of the drug.

Injected intrathecally, tetracaine produces a significant increase in spinal cord blood flow, an effect that can be prevented or reversed by epinephrine.¹⁵⁷ Vasodilation is less prominent with lidocaine, and bupivacaine produces vasoconstriction. Predictably, vasoconstrictors appear to be most effective in prolonging tetracaine-induced spinal anesthesia (up to 100%) and less effective at prolonging lidocaine spinal anesthesia, whereas the effect on bupivacaine spinal anesthesia remains controversial and is, at best, minimal.

Physiologic Effects

The goal of spinal anesthesia is to provide sensory anesthesia and skeletal muscle relaxation. It is the accompanying level of sympathetic nervous system blockade, however, that produces physiologic alterations.

Cardiac Arrest

Cardiac arrest may accompany hypotension and bradycardia associated with spinal anesthesia.^{85,158,159} Risk factors for hypotension include sensory anesthesia above T5 and baseline systolic blood pressure of <120 mm Hg. Risk factors for bradycardia include sensory anesthesia above T5, baseline heart rate <60 beats per minute, prolonged P-R interval on the electrocardiogram, and concomitant treatment with β-blocking drugs. Common features of cardiac arrest in patients receiving spinal anesthesia have included administration of sedation to produce a sleeplike state without spontaneous verbalization and lack of early administration of epinephrine. Even when therapy is promptly administered, patients may be refractory to treatment because local anesthetic-induced sympathetic nervous system blockade, which decreases circulating blood volume, may also cause a defective neuroendocrine response to stress. Even early administration of epinephrine in patients being previously monitored with pulse oximetry and capnography may not guarantee a good outcome following neuraxial cardiac arrest.⁸⁵

Sympathetic nervous system blockade results in arteriolar dilatation, but systemic blood pressure does not decrease proportionally because of compensatory vasoconstriction in areas with intact sympathetic nervous system innervation. Compensatory vasoconstriction occurs principally in the upper extremities and does not involve the cerebral vasculature. Even with total sympathetic nervous system blockade produced by spinal anesthesia, the decrease in systemic vascular resistance is <15%. This change is minimal because smooth muscles of arterioles retain intrinsic tone and do not dilate maximally.

The most important cardiovascular responses produced by spinal anesthesia are those that result from changes in the venous circulation. Unlike arterioles denervated by sympathetic nervous system blockade, venules do not maintain intrinsic tone and thus dilate maximally during spinal anesthesia. The resulting increased vascular capacitance decreases venous return to the heart, leading to decreases in cardiac output and systemic blood pressure. The physiologic effect of spinal anesthesia on venous return emphasizes the risk of extreme systemic hypotension if this technique is instituted in hypovolemic patients. Blockade of preganglionic cardiac accelerator fibers (T1-T4) results in heart rate slowing, particularly if decreased venous return and central venous pressure decrease the stimulation of intrinsic stretch receptors in the right atrium (Bezold-Jarisch reflex). For example, heart rate will increase with a head-down position that increases venous return and central venous pressure to stimulate these receptors. During spinal anesthesia, myocardial oxygen requirements are decreased as a result of decreased heart rate, venous return, and systemic blood pressure.

Apnea

Apnea that occurs with an excessive level of spinal anesthesia probably reflects ischemic paralysis of the medullary ventilatory centers due to profound hypotension and associated decreases in cerebral blood flow. Concentrations of local anesthetics in ventricular cerebrospinal fluid are usually too low to produce pharmacologic effects on the ventilatory centers. However, rarely phrenic nerve which originates from anterior rami of C3-C5 nerve roots, can be paralyzed.

Analgesia

Lidocaine and procaine have been demonstrated to produce intense analgesia when injected IV. Use of local anesthetics for this purpose, however, is limited by the small margin of safety between IV analgesic doses and those that produce systemic toxicity. Nevertheless, continuous low-dose infusion of lidocaine to maintain a plasma concentration of 1 to 2 µg/mL decreases the severity of postoperative pain and decreases requirements for opioids without producing systemic toxicity.¹⁶⁰ Lidocaine administered IV also decreases anesthetic requirements for volatile drugs.¹⁶¹ Lidocaine may also be administered IV in the perioperative period as a cough suppressant. In this regard, the cough reflex during intubation of the trachea is suppressed by plasma concentrations of lidocaine >2 µg/mL.¹⁶² Stump pain (neuromas) but not phantom pain (cortical reorganization) following amputation is diminished by IV administration of lidocaine.¹⁶³ Lidocaine infusion during surgery may be a useful analgesic adjunct for patients undergoing open and laparoscopic colorectal surgeries and has shown to improve pain scores, reduce opioid consumption, and reduce length of hospital stay. However, according to a recent Cochrane review, it is uncertain if lidocaine improves pain scores or gastrointestinal recovery, postoperative nausea, and opioid consumption in the early postoperative phase.¹⁶⁴

Suppression of Ventricular Cardiac Dysrhythmias

In addition to suppressing ventricular cardiac dysrhythmias, the IV administration of lidocaine may increase the defibrillation threshold. Failure to recognize this effect could lead to unnecessary revision of the lead system of an implantable cardioverter defibrillator.¹⁶⁵

Antiinflammatory Effects

Local anesthetics modulate inflammatory responses and may be useful in mitigating perioperative inflammatory injury.¹⁰⁷ For example, overreactive inflammatory responses that destroy rather than protect are critical in the development of several perioperative phenomena including postoperative pain, adult respiratory distress syndrome, systemic inflammatory response syndrome, and multiple organ failure. Beneficial effects attributed to epidural anesthesia (pain relief, decreased thrombosis from hypercoagulability) may reflect

antiinflammatory effects of local anesthetics. Adverse effects of local anesthetic-induced antiinflammatory effects include retardation of wound healing and increased risk of infection. Nevertheless, there is evidence that local anesthetics also possess significant antibacterial effects (tetracaine > bupivacaine > lidocaine).¹⁶⁶ The IV lidocaine is being postulated to decrease perioperative stress and improve anesthetic depth. Effect on depth of anesthesia, of IV lidocaine, as measured by bispectral index is studied in the presence or absence of midazolam. The IV lidocaine decreases bispectral index by modulating the effect of midazolam.¹⁶⁷

Mechanism

Antiinflammatory effects of local anesthetics are not dependent on the sodium ion channel blockade that is responsible for the anesthetic effects of these drugs. Local anesthetics may modulate inflammatory responses by inhibiting inflammatory mediator signaling. For example, local anesthetics inhibit platelet-activating factor (an inflammatory mediator), which is an established signaling mechanism in early acute respiratory distress syndrome, a typical postoperative inflammatory disorder.¹⁶⁸ Many of the mediators (thrombin, thromboxane, platelet-activating factor, and interleukins) of the inflammatory and hemostatic systems act through G protein-coupled receptors. Local anesthetics may inhibit G proteins, resulting in antiinflammatory effects.¹⁶⁹ In addition, local anesthetics inhibit neutrophil accumulation at sites of inflammation and impair free radical and mediator release.¹⁷⁰ Local anesthetics in clinically relevant concentrations inhibit superoxide anion production of platelet-activating factor-primed neutrophils.¹⁶⁸ Priming is the process whereby the response of neutrophils to a subsequent activating stimulus is potentiated. Levobupivacaine is more effective than bupivacaine and other local anesthetics in suppressing neutrophil priming.¹⁷¹ Decreased generation of reactive oxygen radicals is associated with decreases in ischemic damage after myocardial infarction.

Bronchodilation

Inhaled lidocaine and ropivacaine attenuate histamine-induced bronchospasm and induce airway anesthesia. This response most likely reflects topical airway anesthesia, as bronchial reactivity is inhibited at plasma concentrations that are lower than those needed to attenuate bronchial reactivity. Nevertheless, dyclonine, a longer lasting and more intense local anesthetic, does not reliably attenuate bronchial hyperreactivity, suggesting that other properties of local anesthetics may be important.¹⁷²

Liposomal Local Anesthetics

Various formulation and drug delivery system including liposomes, cyclodextrins, and biopolymers are intended to prolong the duration and to limit the toxicity of local anesthetics. The goal is to upload higher amount of local anesthetic into the molecule and to have a consistent release of local anesthetic in the tissues.¹⁷³ Liposomes, hydrophobic-based polymer particles such as poly(lactic-co-glycolic acid) microspheres, and solid polymers like poly(sebacic-co-ricinoleic acid) P(SA:RA) and their combination with synthetic and natural local anesthetic are examples of delivery systems currently in development or in clinical use.¹⁷⁴

Drugs such as lidocaine, tetracaine, and bupivacaine have been incorporated into liposomes to prolong the duration of action and decrease toxicity.¹⁷⁵ Currently, liposomal bupivacaine is indicated for single-dose infiltration in adults to produce postsurgical local analgesia and as an interscalene brachial plexus nerve block to produce postsurgical regional analgesia.¹⁷⁶⁻¹⁷⁸ Liposomal bupivacaine consists of microscopic, spherical, and multivesicular liposomes, and each liposome particle is composed of a honeycomb-like structure of numerous internal aqueous chambers. Lipid membranes separate these aqueous chambers that contain encapsulated bupivacaine. Bupivacaine is released from the liposome particles by a complex mechanism over an extended period (up to 96 hours). Mixing liposomal bupivacaine with nonbupivacaine-based local anesthetics, including lidocaine, is not recommended. It may cause an immediate release of bupivacaine from liposomes and may cause toxicity. Although the use of liposomal bupivacaine has exponentially increased in all surgery settings, the clear evidence of benefit when compared to much cheaper plain bupivacaine is lacking.

In a randomized, double-blind, placebo-controlled, parallel-group study, liposomal bupivacaine demonstrated a statistically significant reduction in pain through 72 hours, decreased opioid requirements, delayed time to first opioid use, and improved patient satisfaction compared with placebo after hemorrhoidectomy (Figure 10.16).¹⁷⁸ Liposomal bupivacaine is also been studied for use in nerve blocks,¹⁷⁹ intraoperative administration in ileostomy reversal,¹⁸⁰ but the results are inconclusive due to smaller sample size.

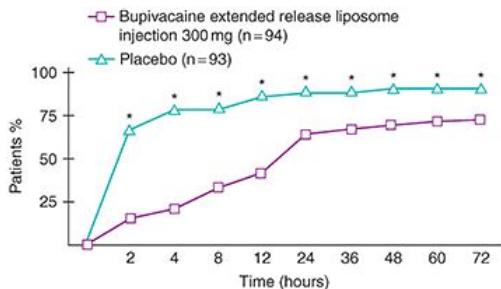


FIGURE 10.16 Time to first use of opioid rescue medication (percentage of patients) after surgery. Gorfine SR, Onel E, Patou G, Krivokapic ZV. *Bupivacaine extended-release liposome injection for prolonged postsurgical analgesia in patients undergoing hemorrhoidectomy: a multicenter, randomized, double-blind, placebo-controlled trial*. Dis Colon Rectum. 2011;54(12):1552-1559.

In a systematic review of 11 studies, periarticular liposomal bupivacaine infiltration resulted in similar pain control and functional recovery after total knee arthroplasty, compared to peripheral nerve blocks or periarticular blocks using traditional local anesthetic.¹⁸¹ However, appropriate use of liposomal bupivacaine for local infiltration analgesia compared to plain bupivacaine for total knee surgery improved postsurgical pain, opioid consumption, and time to first opioid rescue.¹⁸² When comparing all techniques, liposomal bupivacaine was not associated with a clinically relevant improvement in inpatient opioid prescription, resource utilization, or opioid-related complications in patients who received modern pain management including a peripheral nerve block.¹⁸³

In a prospective evaluation of hip arthroscopy patients, postoperative pain scores and opioid use was similar with either liposomal bupivacaine or plain bupivacaine fascia iliaca block.¹⁸⁴ Overall, a Cochrane review of 10 randomized trial summarized the current evidence as costly, “liposomal bupivacaine use at the surgical site does appear to reduce postoperative pain compared to placebo, however, at present the limited evidence does not demonstrate superiority to bupivacaine hydrochloride.”¹⁸⁵

Tumescent Liposuction

Tumescent technique for liposuction characterizes the subcutaneous infiltration of large volumes (5 L or more) of solution containing highly diluted lidocaine (0.05% to 0.10%) with epinephrine (1:100,000). The taut stretching of overlying blanched skin by the large volume of solution and epinephrine-induced vasoconstriction is the origin of the term **tumescent technique**.

The result is sufficient local anesthesia for the liposuction, virtually bloodless aspirates, and prolonged postoperative analgesia. Slow and sustained release of lidocaine into the circulation is associated with plasma concentrations <1.5 µg/mL that peak 12 to 14 hours after injection and then decline gradually over the next 6 to 14 hours.¹⁸⁶ Plasma concentrations of epinephrine peak at 3 to 5 times the upper normal limits approximately 3 hours following injection of the solution and return to normal after about 12 hours.¹⁸⁷ The recommended adult dose of lidocaine with epinephrine for regional anesthesia is about 7 mg/kg. When highly diluted lidocaine solutions are administered for tumescent liposuction, the dose of lidocaine may range from 35 to 55 mg/kg (“mega-dose lidocaine”).¹⁸⁸ It is estimated that 1 g of subcutaneous tissue can absorb up to 1 mg of lidocaine (“tissue buffering system”). The injection of additional undiluted lidocaine for concomitant cosmetic procedures must be considered in estimating the likely plasma concentrations of lidocaine that will occur.

Tumescent liposuction is commonly used in aesthetic contouring of thigh, abdomen, hip and buttocks, and its use is increasing in reconstructive plastic surgery procedures. Despite the popularity and presumed safety of tumescent liposuction, there are reports of increased mortality associated with this technique (greater than mortality associated with automobile accidents).¹⁸⁹ Causes of death may include lidocaine toxicity or local anesthetic-induced depression of cardiac conduction and contractility. Overall complication rate in a nationwide quality improvement study was 0.7%, in which 0.57% were minor complications and 0.14% were major complications.^{190,191}

Cocaine Toxicity

Cocaine abuse and intoxication is widespread across the globe. In the United States, 1.5 million (2010) adults use cocaine; in Europe, 4 million (2009) adults use cocaine.¹⁹² Cocaine produces sympathetic nervous system stimulation by blocking the presynaptic uptake of norepinephrine and dopamine, thus increasing their postsynaptic concentrations. Because of this blocking effect, dopamine remains at high concentrations in the synapse and continues to affect adjacent neurons, producing the characteristic cocaine “high.”^{193,194} Chronic exposure to cocaine is postulated to affect adversely dopaminergic function in the brain due to dopamine depletion.

Pharmacokinetics

Once cocaine is absorbed, the pharmacokinetics, regardless of the route of administration, are similar.¹⁹⁵ Conversely, the route of administration is important in the rate of onset as well as the intensity and duration of cocaine’s effects. For example, peak venous plasma concentrations of cocaine are achieved at approximately 30 to 40 minutes after intranasal administration and approximately 5 minutes after IV and smoked cocaine administration. The maximum physiologic effects of intranasal cocaine occur within 15 to 40 minutes, and the maximum subjective effects occur within 10 to 20 minutes. The duration of effects is approximately 60 minutes or longer after peak effects. The subjective effects occur within minutes of IV or smoked cocaine use, and the duration of effect is approximately 30 to 45 minutes. The elimination half-time of cocaine is 60 to 90 minutes, and metabolism is principally by plasma esterases (see “[Metabolism of Ester Local Anesthetics](#)” section). Urinary excretion of unchanged cocaine (<1% of the total dose) and metabolites (benzoylecgonine and ecgonine methyl ester representing about 65% of the dose) is similar regardless of the route of administration.

Adverse Physiologic Effects

Acute cocaine administration has local anesthetic, vasoconstrictive, and sympathomimetic effects. Cardiac function is adversely affected, and cocaine is known to cause coronary vasospasm, myocardial ischemia, myocardial infarction, and ventricular cardiac dysrhythmias, including ventricular fibrillation.¹⁹⁶ Associated hypertension and tachycardia further increase myocardial oxygen requirements at a time when coronary oxygen delivery is decreased by the effects of cocaine on coronary blood flow. Even remote cocaine use can result in myocardial ischemia and hypotension for as long as 6 weeks after discontinuing cocaine use.^{197,198} Presumably, delayed episodes of myocardial ischemia are due to cocaine-induced coronary artery vasospasm. Excessive sensitivity of the coronary vasculature to catecholamines after chronic exposure to cocaine may be due in part to cocaine-induced depletion of dopamine activity. Cocaine-abusing parturients are at higher risk for interim peripartum events such as hypertension, hypotension, and wheezing episodes.¹⁹⁹

Cocaine may produce hyperpyrexia, which can contribute to seizures. Unexpected patient agitation in the perioperative period may reflect the effects of cocaine ingestion.²⁰⁰ There is a temporal relationship between the recreational use of cocaine and cerebrovascular accidents.²⁰¹

Treatment

Nitroglycerin has been used to treat cocaine-induced myocardial ischemia.²⁰² β -Adrenergic blockade accentuates coronary artery vasospasm in the setting of acute cocaine overdose.^{203,204} Whether β -adrenergic blockade is harmful for coronary vasospasm in the setting of chronic cocaine use is not known. Furthermore,

administration of β -blocking drugs in the presence of catecholamine-induced hypertension and tachycardia has been associated with profound cardiovascular collapse and cardiac arrest that is unresponsive to aggressive cardiopulmonary resuscitation.²⁰⁵ Thus, β blockers should be used with caution. In this situation, administration of a vasodilating drug such as nitroprusside may be the safest intervention. α -Adrenergic blockade may be effective in treatment of coronary vasoconstriction due to cocaine, but in the presence of hypotension, this intervention is questionable.

In 2008, American Heart Association published a statement for management of cocaine-associated chest pain and myocardial infarction (Figure 10.17).²⁰⁶ In addition to their beneficial effect in seizure control, benzodiazepines also help in acute coronary syndromes by relieving chest pain and improving hemodynamic profile. Nitroglycerin and phentolamine is useful in reversing coronary vasoconstriction.

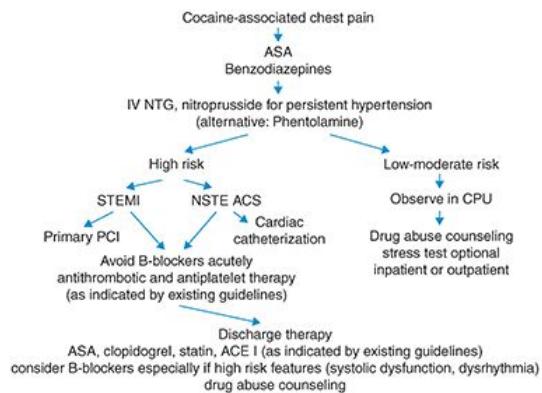


FIGURE 10.17 Therapeutic and diagnostic recommendations in cocaine-associated chest pain.²⁰⁶ ACE I, angiotensin-converting enzyme inhibitor; ASA, acetylsalicylic acid; CPU, chest pain unit; IV NTG, intravenous nitroglycerin; NSTE ACS, non-ST-segment elevation acute coronary syndrome; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

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Neuromuscular Physiology

Mohamed A. Naguib[†]

The mammalian neuromuscular junction (NMJ) is one of the most studied and best understood synapses.¹ The NMJ is a synapse that develops between a motor neuron and a muscle fiber and is made up of several components: the presynaptic nerve terminal, the postsynaptic muscle membrane on the muscle membrane, and the intervening cleft (or gap). In the 19th century and early years of the 20th century, there was broad support for the concept that impulses in the nerves acted directly on muscle, resulting in muscular contraction—the “electrical theory.” This theory was eventually refuted with the discovery of the role of acetylcholine in neuromuscular transmission,^{2,3} and in 1936, the Nobel Prize in Physiology or Medicine was awarded to Sir Henry Hallett Dale and Otto Loewi “for their discoveries relating to chemical transmission of nerve impulses.” This was followed by the discovery that a muscle membrane-bound allosteric protein, the nicotinic acetylcholine receptor (nAChR).⁴

Muscle Types

Muscle is generally classified as skeletal, smooth, or cardiac. Both skeletal and cardiac muscles are striated muscles sharing a common basic organization of the contractile filaments. There are, however, distinct histologic and functional differences between these two muscles. Skeletal muscle cells are multinucleated and tubular in shape, whereas cardiac muscle cells may be mono- or binucleated, are branched, and contain intercalated discs. Skeletal muscle is responsible for voluntary actions, whereas smooth and cardiac muscles subserve functions related to the cardiovascular, respiratory, gastrointestinal, and genitourinary systems. Muscle composes 45% to 50% of total body mass, with skeletal muscles accounting for approximately 40% of body mass. An estimated 250 million cells are present in more than 400 skeletal muscles of humans. Muscle cells are highly specialized cells for the conversion of chemical energy into mechanical energy. Inappropriate activity of smooth muscle is involved in many illnesses including hypertension, atherosclerosis, asthma, and disorders of the gastrointestinal tract.

Motor Units

Vertebrate skeletal muscles are innervated by large myelinated α motor neurons that originate from cell bodies located in the brainstem or ventral (anterior) horns of the spinal cord ([Figure 11.1](#)).⁵ The myelinated nerve axon reaches the muscle through mixed peripheral nerves. Motor nerves branch in the skeletal muscle with each nerve terminal innervating a single muscle cell.

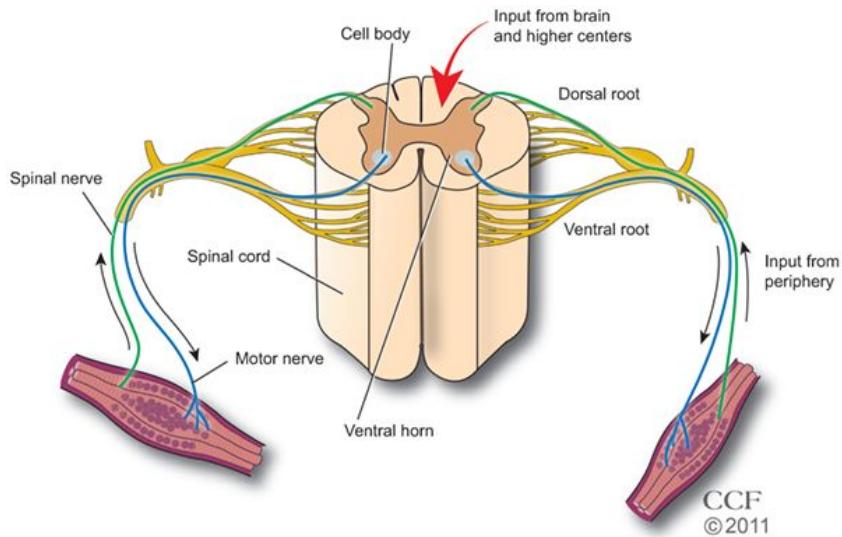


FIGURE 11.1 Schematic depiction of skeletal muscle innervation. Reprinted with permission from Cleveland Clinic Center for Medical Art & Photography. Copyright © 2011-2020. All Rights Reserved.

The motor unit is the functional contractile unit and is composed of a single myelinated α motor neuron and all muscle fibers that receive innervation from this single neuron. Motor units vary in size. A large motor nerve innervates more muscle fibers than a smaller motor nerve does. In general, small motor units innervate the “red slow” muscle fibers, whereas large motor units innervate the “white or pale fast” muscle fibers. The slow muscle fibers appear red (eg, masseters) as a result of high contents of myoglobin, mitochondria, and capillaries compared with white muscle fibers (eg, psoas muscle). Unlike the white muscle fibers, the red fibers are resistant to fatigue.⁶ Muscles contain a varying mixture of motor units depending on their function.

The Neuromuscular Junction

The NMJ comprises portions of three structures—motor neuron, muscle fiber, and glial cells known as Schwann cell. The NMJ is a highly specialized synapse at which presynaptic motor nerve endings meet the postsynaptic membranes of skeletal muscles (motor end plates) ([Figure 11.2](#)). The formation, differentiation, and function of the NMJ require a proper interaction (cross talk) between the nerve terminal and muscle cell (for a review, see Naguib et al¹). Failure of this cross talk will result in a wide spectrum of neuromuscular disorders. It should be noted that in early postnatal period, muscle fibers are innervated by multiple motor nerves. It has been shown in mice that on the second postnatal day, approximately 75% of muscle fibers are multiply innervated (>95% by two axons).⁷ However, the transition from multiple to single innervation at the NMJ occurs within few days.⁷ The motor nerve ending branches to form a complex of nerve terminals that invaginate into the skeletal muscle fiber but lie outside the sarcolemma. As each motor neuron approaches its target muscle fiber, it loses its myelin sheath and makes a contact with a single muscle fiber to form an NMJ. The naked motor nerve terminal that is not in contact with the muscle fiber is capped by Schwann cells, providing it with physical integrity by insulating it from the environment and supplying it with nutrients and removing waste products. The importance of glial (Schwann) cells for development, survival, and repair of several aspects of NMJ is addressed elsewhere.^{1,8}

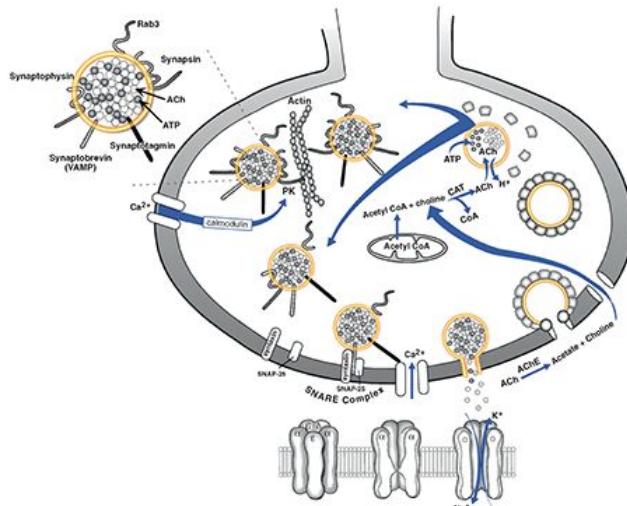


FIGURE 11.2 The synaptic vesicle (SV) exocytosis-endocytosis cycle. After an action potential and calcium ion (Ca^{2+}) influx, phosphorylation of synapsin is activated by calcium-calmodulin activated protein kinases I and II. This results in the mobilization of SVs from the cytomatrix toward the plasma membrane. The formation of the soluble N-ethylmaleimide sensitive factor (NSF) attachment **protein** receptor (SNARE) complex is an essential step for the docking process. After fusion of SVs with the presynaptic plasma membrane, acetylcholine (ACh) is released into the synaptic cleft. Some of the released ACh molecules bind to the nicotinic acetylcholine receptors on the postsynaptic membrane, whereas the rest is rapidly hydrolyzed by the acetylcholinesterase (AChE) present in the synaptic cleft to choline and acetate. Choline is recycled into the terminal by a high-affinity uptake system, making it available for the resynthesis of ACh. Exocytosis is followed by endocytosis in a process dependent on the formation of a clathrin coat and of action of dynamin. After recovering of SV membrane, the coated vesicle uncoats and another cycle starts again. See text for details. Abbreviations: ATP, adenosine triphosphate; CAT, choline acetyltransferase; CoA, coenzyme A; H^+ , hydrogen ion; K^+ , potassium ion; Na^+ , sodium ion; PK, protein kinase; SNAP-25, synaptosomal nerve-associated protein 25 kDa; VAMP, vesicle-associated membrane protein. Reprinted with permission from Naguib M, Flood P, McArdle JJ, et al. Advances in neurobiology of the neuromuscular junction: implications for the anesthesiologist. *Anesthesiology*. 2002;96(1):202-231. Copyright © 2002 American Society of Anesthesiologists, Inc.

The NMJ is designed to transmit electrical impulses from the nerve terminal to the skeletal muscle via the chemical transmitter, acetylcholine. Structurally, the NMJ is consisted of a three components: (1) the *presynaptic* (or prejunctional) nerve terminal containing synaptic vesicles (SVs) (filled with acetylcholine) and mitochondria; (2) the *synaptic cleft* that contains basal lamina to which acetylcholinesterase enzyme responsible for hydrolysis of free acetylcholine is attached; and (3) the *postsynaptic* (or postjunctional) muscle membrane that opposes the nerve terminal is highly infolded and these folds are called secondary folds (or secondary postsynaptic cleft). Membrane infoldings increase the surface area of the muscle plasma membrane in the postsynaptic region (see [Figure 11.6](#)). The nAChRs are concentrated at the crests of these folds (directly opposing the *active zones* of the presynaptic membrane in which SVs are clustered), and voltage-gated sodium channels are present in the troughs of the folds.

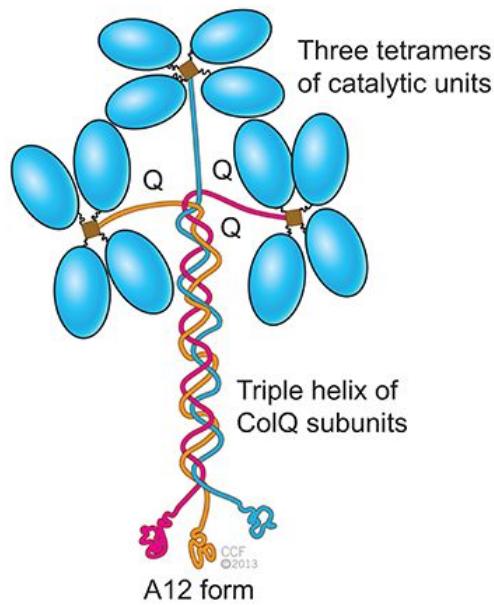


FIGURE 11.3 Structure of acetylcholinesterase.

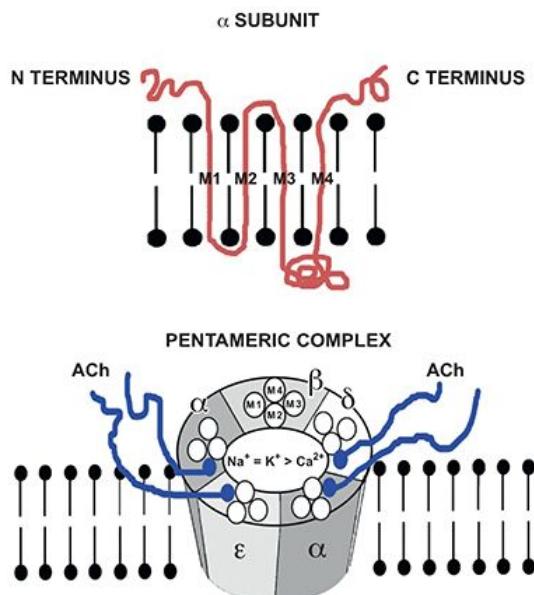


FIGURE 11.4 Subunit composition of the nicotinic acetylcholine receptor (nAChR) in the endplate surface of adult mammalian muscle. The adult AChR is an intrinsic membrane protein with five distinct subunits ($\alpha\beta\delta\epsilon$). Each subunit contains four helical domains labeled M1 to M4. The M2 domain forms the channel pore. The upper panel shows a single α subunit with its N and C termini on the extracellular surface of the membrane lipid bilayer. Between the N and C termini, the α subunit forms four helices (M1, M2, M3, and M4), which span the membrane bilayer. The lower panel shows the pentameric structure of the nAChR of adult mammalian muscle. The N termini of two subunits cooperate to form two distinct binding pockets for acetylcholine (ACh). These pockets occur at the ϵ - α and the δ - α subunit interface. The M2 membrane spanning domain of each subunit lines the ion channel. The doubly liganded ion channel has equal permeability to sodium ion (Na^+) and potassium ion (K^+); calcium ion (Ca^{2+}) contributes approximately 2.5% to the total permeability. Reprinted with permission from Naguib M, Flood P, McArdle JJ, et al. *Advances in neurobiology of the neuromuscular junction: implications for the anesthesiologist*. Anesthesiology. 2002;96(1):202-231. Copyright © 2002 American Society of Anesthesiologists, Inc.

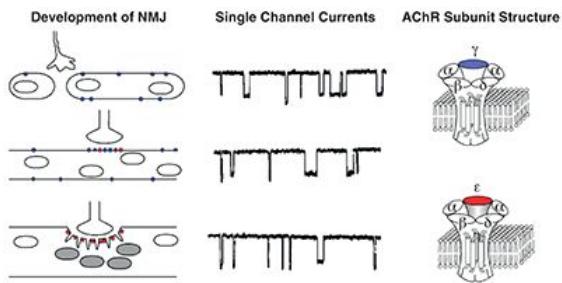


FIGURE 11.5 Development of the neuromuscular junction (NMJ). Left, Motor neuron growth cones contact myotubes as they fuse from myoblasts and express mostly fetal nicotinic acetylcholine receptors (nAChRs; marked in blue) in their surface membranes. In adult muscle, adult nAChRs (marked in red) predominate and are largely concentrated at the NMJ. Center, Records of acetylcholine receptor (AChR) channel openings from muscle membranes at different stages of neuromuscular development. Fetal (top) and adult nAChRs (bottom) are activated by acetylcholine to form ion channels of different conductance and gating properties. Right, Subunit composition of fetal and adult AChR subtypes. Fetal and adult AChR subtypes are characterized by the presence of a γ and ϵ subunit, respectively. *Reprinted with permission from Naguib M, Flood P, McArdle JJ, et al. Advances in neurobiology of the neuromuscular junction: implications for the anesthesiologist. Anesthesiology. 2002;96(1):202-231. Copyright © 2002 American Society of Anesthesiologists, Inc.*

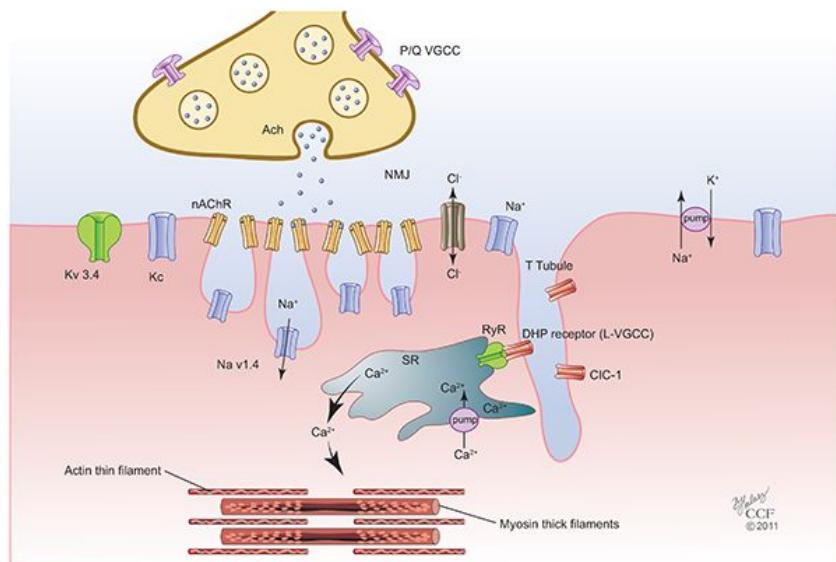


FIGURE 11.6 Neuromuscular transmission and excitation-contraction coupling. Abbreviations: Ach, acetylcholine; Ca^{2+} , calcium ion; CIC-1, voltage gated chloride channel 1; Cl^- , chloride; DHP receptor, dihydropyridine receptor; K^+ , potassium ion; Kc, calcium activated potassium channel; L-VGCC, L type voltage gated potassium channel; Na^+ , sodium ion; nAChR, nicotinic acetylcholine receptor; NMJ, neuromuscular joint; P/Q VGCC, voltage-gated calcium channel (P/Q type); RyR, ryanodine receptor; SR, sarcoplasmic reticulum. *Reprinted with permission from Cleveland Clinic Center for Medical Art & Photography. Copyright © 2011-2020. All Rights Reserved.*

The plasticity of neuromuscular transmission is dependent on a highly orchestrated mechanism involving (1) synthesis, storage, and release of acetylcholine from the presynaptic region at the NMJ; (2) binding of acetylcholine to nicotinic receptors on the muscle membrane (postsynaptic region) and generation of action potentials; (3) rapid hydrolysis of acetylcholine by the enzyme acetylcholinesterase, which is

present in the synaptic cleft; and (4) adaptation of the muscle contractile proteins to functional demands.¹ Synaptic plasticity is the “ability of individual synaptic junctions to respond [ie, to change in strength in response] to either use or disuse.”⁹

Presynaptic Region

Synaptic Vesicles

The SVs are specialized secretory organelles (see [Figure 11.2](#)). The SVs are synthesized in the neuronal cell body in the endoplasmic reticulum and transported to the nerve terminal via the microtubule system. The SVs are then loaded with acetylcholine in the motor nerve endings. Acetylcholine is first synthesized in the cytoplasm of the nerve terminal from acetyl coenzyme A and choline in a reaction catalyzed by the soluble enzyme choline acetyltransferase. An energy-dependent “transporter” then accumulates acetylcholine within vesicles. Each vesicle contains 5,000 to 10,000 molecules of acetylcholine. The acetylcholine contained in a single vesicle is often referred to as a “quantum” of transmitter. The SVs possess a diverse set of specialized proteins that can be divided into two functional classes: proteins involved in the uptake of neurotransmitters (transport proteins) and proteins that mediate SV membrane traffic such as docking, fusion, and budding (for review, see Naguib et al¹). Calcium ion signaling plays a pivotal role in the process of acetylcholine vesicles exocytosis (see [Figure 11.2](#)). There are two pools of vesicles that differ in the probability of mobilization to the active site: a readily releasable store (active pool) and a reserve store. The active pool is aligned near the active zones.

The miniature endplate potential amplitude represents the depolarization of the postsynaptic membrane produced by the contents of a single vesicle. The endplate potential results from summation of miniature endplate potential produced by acetylcholine contents of ~50 to 300 SVs. Nearly 50% of the released acetylcholine is rapidly hydrolyzed by the acetylcholinesterase during diffusion across the synaptic cleft before reaching the postsynaptic receptors. The products of this hydrolysis are choline and acetate. Choline is recycled into the terminal by a high-affinity uptake system, making it available for the resynthesis of acetylcholine. After exocytosis, the membrane components of the SVs are recovered by endocytosis and recycled for future use.

Synaptic Cleft

The synaptic cleft is ~20 to 50 nm wide. It separates nerve and muscle fiber plasma membranes and is encompasses the synaptic basal lamina and is filled with extracellular fluid. Acetylcholinesterase enzyme is bound to the basal lamina at the cleft ([Figure 11.3](#)).

Acetylcholinesterase ranks as one of the most efficient catalytic processes known. The efficiency of acetylcholinesterase depends on its fast activity. It can catalyze acetylcholine hydrolysis (4,000 molecules of acetylcholine hydrolyzed per active site per second) at near diffusion-limited rates.¹⁰ Acetylcholinesterase is highly concentrated at the NMJ but present in a lower concentration throughout the length of muscle fibers.¹¹ Acetylcholinesterase is regulated, in part, by muscle activity and by the spontaneous or nerve-evoked depolarization of the plasma membrane.¹² After denervation, there is a large decrease in the density of acetylcholinesterase molecules. In addition to hydrolysis of acetylcholine, acetylcholinesterase has other functions such as nerve growth-promoting activities¹³ and modulation of nAChRs.

The Nicotinic Acetylcholine Receptor at the Neuromuscular Junction

In the adult mammalian skeletal muscle, the nAChRs are highly concentrated (~10,000/ μm^2) at the crests of junctional folds and in close proximity to acetylcholine-releasing sites. The AChR expression and clusters are both regulated by positive and negative signals from the nerve and muscle. The nAChR is a pentameric complex of two α subunits in association with a single β , δ , and ϵ subunit ([Figure 11.4](#)). These subunits are organized to form a transmembrane pore (a channel) as well as the extracellular binding pockets for acetylcholine and other agonists or antagonists.¹ Each of the two α subunits has an acetylcholine-binding site. These sites are proteins located in pockets approximately 3.0 nm above the surface membrane at the interfaces of the α - ϵ and α - δ subunits.¹⁴ The fetal nAChRs are different from postnatal ones in composition

and electric properties. It contains a γ subunit instead of an ϵ adult subunit. The mature nAChR has shorter burst duration and a higher conductance to sodium ion, potassium ion (K^+), and calcium ion than the fetal nAChR.^{1,15}

The fetal nAChR is a low-conductance channel in contrast to the high-conductance channel of the adult nAChR ([Figure 11.5](#)). Thus, acetylcholine release causes brief activation and reduced probability of channel opening.¹ Upregulation of nAChRs, found in states of functional or surgical denervation, is characterized by the spreading of predominantly fetal type nAChRs. These receptors are resistant to nondepolarizing neuromuscular blockers and more sensitive to succinylcholine (SCh).¹⁶ When depolarized, the immature isoform has a prolonged open channel time that exaggerates the K^+ efflux.¹⁷

Simultaneous binding of two acetylcholine molecules to the extracellular N-terminal domain of the two α subunits of nAChRs initiates conformational changes that open a channel through the center of the receptor, allowing sodium and calcium ions to move into the skeletal muscle and K^+ to leave. Each NMJ contains several million postjunctional receptors, and a burst of acetylcholine from the nerve ending opens at least 400,000 receptors. As a result, sufficient current flows through these open receptors to depolarize the endplate and create the action potential that triggers contraction of the skeletal muscle. It is the flow of ions that is the basis of normal neuromuscular transmission.

The two α subunits, in addition to being the binding sites for acetylcholine, are occupied by neuromuscular-blocking drugs. Nondepolarizing neuromuscular-blocking drugs bind to one or both α subunits but, unlike acetylcholine, lack agonist activity (competitive blockade). As a result, conformational changes do not occur, and the receptor channel remains closed. Therefore, ions do not flow through these channels, and depolarization cannot occur at these sites. If enough channels remain closed, there is blockade of neuromuscular transmission. A nondepolarizing neuromuscular-blocking drug may show preference for one of the two α subunits. This may result in synergism if two nondepolarizing neuromuscular-blocking drugs with different selective preferences for each α subunit are administered simultaneously.^{18,19} The probability of binding is dependent on the concentration of acetylcholine and nondepolarizing neuromuscular-blocking drug at the receptor and the affinity of the receptor for the neurotransmitter or drug. When the neuromuscular-blocking drug diffuses from the nAChRs, the probability of receptor binding of acetylcholine increases, and the effect of the nondepolarizing neuromuscular-blocking drug decreases.

The SCh, which is structurally two molecules of acetylcholine bound together, is a partial agonist at nAChRs and depolarizes (opens) the ion channels. This opening requires the binding of only one molecule of SCh to the α subunit. The other α subunit can be occupied by either acetylcholine or SCh. Because SCh is not hydrolyzed by acetylcholinesterase, the channel remains open for a longer period of time than would be produced by acetylcholine, resulting in a depolarizing block (sustained depolarization prevents propagation of an action potential). Furthermore, SCh can diffuse from nAChRs and repeatedly bind to other nAChRs until it is cleared from the area of the NMJ and is exposed to hydrolysis by plasma cholinesterase. Plasma cholinesterase has a distinct molecular structure and function from acetylcholinesterase.

Large doses of nondepolarizing neuromuscular-blocking drugs may also prevent normal flow of ions by entering the channels formed by nAChRs to produce blockade within the channel. Similar blockade of sodium ion channels is produced by local anesthetics.

Neuromuscular Transmission and Excitation-Contraction Coupling

- 1. Motor nerve**
 - a.** Depolarization of the motor nerve will open the voltage-gated calcium ion channels that trigger both mobilization of SVs and the fusion machinery in the nerve terminal to release acetylcholine.
 - b.** Several forms of K^+ channel present in the nerve terminal serve to limit the extent of calcium ion entry and transmitter release (ie, initiate repolarization of nerve terminal).²⁰
- 2. Muscle**
 - a.** The released acetylcholine binds to α subunits of the nAChRs. These ligand-gated cation channels open almost instantaneously when two acetylcholine molecules bind cooperatively to sites on the

extracellular surface of the protein, causing a conformational shift in the subunits. When the channel opens, sodium ions flow down their electrochemical gradient and into the muscle cell and depolarize the muscle cell membrane at the NMJ, whereas potassium simultaneously exits the cytosol of the fiber.^{20,21}

- b.** This depolarization activates voltage-gated sodium channels that present in the muscle membrane, which mediate the initiation and propagation of action potentials across the surface of the muscle membrane and into the transverse tubules (T tubules) resulting in the upstroke of the action potential.^{20,21,22}
- c.** There are two types of calcium channels, dihydropyridine receptor (DHPR) in the T tubules and the ryanodine receptor 1 (RyR1) in the sarcoplasmic reticulum (SR) (**Figure 11.6**). The DHPRs act as “voltage sensors”^{23,24} and are activated by membrane depolarization, which in turn activate RyR1 receptors.
- d.** DHPR-RyR1 interaction²⁵ releases large amounts of calcium ion from the SR that result in a transient increase in myoplasmic free calcium ion, which binds to troponin C. This initiates movement of tropomyosin on the thin filament (actin) and allows cross-bridges between the myosin with the binding sites on actin, which eventually result in force development. This process is known as excitation-contraction coupling (**Figure 11.7**).²⁶ Shortly after releasing calcium, the SR begins to reaccumulate this ion by an active transport process (calcium pump). This transport mechanism can concentrate calcium up to 2,000-fold inside the SR. Adenosine triphosphate provides the energy for calcium ion transport. Once the calcium concentration in the sarcoplasm has been lowered sufficiently, cross-bridging between myosin and actin ceases and the skeletal muscle relaxes. Failure of the calcium ion pump results in sustained skeletal muscle contraction and marked increases in heat production, leading to malignant hyperthermia. The gene for this calcium ion channel (RyR1) is on chromosome 19. Mutations in this gene are associated with malignant hyperthermia susceptibility in some patients.
- e.** Repolarization of the muscle membrane is initiated by the closing of the sodium channels and by the opening of K⁺ channel that conduct an outward K⁺ current.²⁷
- f.** The return of the muscle membrane potential to its resting level (approximately –70 to –90 mV) is achieved by allowing chloride (Cl[–]) to enter the cell through voltage-sensitive chloride channels.²⁰

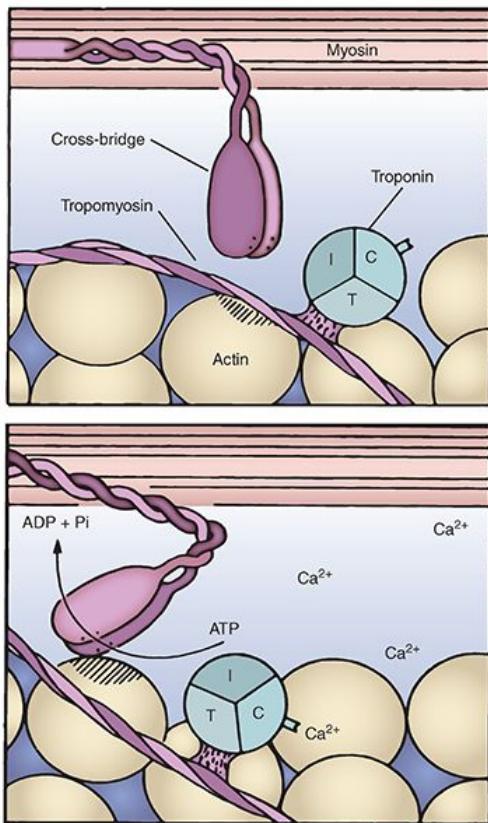


FIGURE 11.7 Contraction of skeletal muscle is initiated by attachment of calcium ions (Ca^{2+}) to troponin, leading to hydrolysis of adenosine triphosphate (ATP) and cross-bridging between actin and myosin. Abbreviation: ADP, adenosine diphosphate; Pi, inorganic phosphate. Republished with permission of McGraw Hill LLC from Ganong WF. Review of Medical Physiology, 21st ed. New York, NY: Lange Medical Books/McGraw Hill, 2003; permission conveyed through Copyright Clearance Center, Inc.

Blood Flow

Skeletal muscle blood flow can increase more than 20 times (a greater increase than in any other tissue of the body) during strenuous exercise.²⁸ At rest, only 20% to 25% of the capillaries are open, and skeletal muscle blood flow is 3 to 4 mL/100 g/min. During strenuous exercise, almost all skeletal muscle capillaries become patent. Opening of previously collapsed capillaries diminishes the distance that oxygen and other nutrients must diffuse from capillaries to skeletal muscle fibers and contributes an increased surface area through which nutrients can diffuse from blood. Presumably, exercise lowers the local concentration of oxygen, which in turn causes vasodilation because the vessel walls cannot maintain contraction in the absence of adequate amounts of oxygen. Alternatively, oxygen deficiency may cause release of vasodilator substances such as K^+ and adenosine. The increase in cardiac output that occurs during exercise results principally from local vasodilation in active skeletal muscles and subsequent increased venous return to the heart.

Exercise is associated with a centrally mediated stimulation of the sympathetic nervous system manifesting as vasoconstriction in nonmuscular tissues and increases in systemic blood pressure. Excessive increases in systemic blood pressure, however, are prevented by vascular vasodilation that occurs in the large tissue mass represented by skeletal muscles. Exceptions to nonmuscular tissue vasoconstriction induced by exercise are the coronary and cerebral circulations. This is teleologically understandable because the heart and brain are essential to the response to exercise, as are the skeletal muscles.

Smooth Muscle

Smooth muscle is distinguished anatomically from skeletal and cardiac muscle because it lacks visible cross-striations (actin and myosin are not arranged in regular arrays). Smooth muscle is categorized as *multiunit* or *visceral* smooth muscle. Multiunit smooth muscle contraction is controlled almost exclusively by nerve signals, and spontaneous contractions rarely occur. Examples of multiunit smooth muscles are the ciliary muscles of the eye, iris of the eye, and smooth muscles of many large blood vessels. Smooth muscle must develop force or shorten to provide motility or to alter the dimensions of an organ.

Smooth muscle cells lack T tubules that provide electrical links to SR. However, the sarcolemma of smooth muscle contains saclike invaginations (caveoli) that may be sites where calcium ions enter the cells through voltage-gated calcium ion channels. Calcium ions are released from the SR into the myoplasm when stimulatory neurotransmitters, hormones, or drugs bind to receptors on the sarcolemma. Calcium ion channels on the SR of smooth muscles include RyR1 (similar to those present in skeletal muscles) and inositol 1,4,5-triphosphate (IP_3)-gated calcium ion channels. Neurotransmitters or hormones that act via receptors in the sarcolemma can activate phospholipase C followed by the generation of the second messenger IP_3 . The IP_3 channels are activated when hormones bind to calcium-mobilizing receptors in the SR in smooth muscle cells.

Visceral smooth muscle is characterized by cell membranes that contact adjacent cell membranes, forming a functional syncytium that often undergoes spontaneous contractions as a single unit in the absence of nerve stimulation. These spontaneous action potentials are particularly prominent in tubular structures, accounting for peristaltic motion in sites such as the bile ducts, ureters, and gastrointestinal tract, especially when they are distended. Plateaus in the action potentials of visceral smooth muscle lasting up to 30 seconds may occur in the ureters and uterus. The normal resting transmembrane potential is approximately -60 mV , which is approximately 30 mV less negative than in skeletal muscles.

In addition to stimulation in the absence of extrinsic innervation, smooth muscles are unique in their sensitivity to hormones or local tissue factors. For example, smooth muscle spasm may persist for hours in response to norepinephrine or antidiuretic hormone, whereas local factors such as lack of oxygen or accumulation of hydrogen ions cause vasodilation. It is believed that local factors and hormones cause smooth muscle contraction by activating the calcium ion transport mechanism. Drugs relax smooth muscle by increasing the intracellular concentration of cyclic adenosine monophosphate or cyclic guanosine monophosphate.

Mechanism of Contraction

Smooth muscles contain both actin and myosin. Smooth muscles are different from skeletal muscles: They are innervated by autonomic neurons and they lack troponin. In contrast to skeletal muscles, in which calcium binds to troponin to initiate cross-bridging, in smooth muscle, the calcium-calmodulin complex activates the enzyme necessary for phosphorylation of myosin. This myosin has ATPase activity, and actin then slides on myosin to produce contraction.

The source of calcium in smooth muscle differs from that in skeletal muscle because the SR of smooth muscle is poorly developed. Most of the calcium that causes contraction of smooth muscles enters from extracellular fluid at the time of the action potential. The time required for this diffusion is 200 to 300 milliseconds, which is approximately 50 times longer than for skeletal muscles. Subsequent relaxation of smooth muscles is achieved by a calcium ion transport system that pumps these ions back into extracellular fluid or into the SR. This calcium ion pump is slow compared with the SR pump in skeletal muscles. As a result, the duration of smooth muscle contraction is often seconds rather than milliseconds as is characteristic of skeletal muscles.

Smooth muscles, unlike skeletal muscles, do not atrophy when denervated, but they do become hyperresponsive to the normal neurotransmitter. This denervation hypersensitivity is a general phenomenon that is largely due to synthesis or activation of more receptors.²⁹

An NMJ that is similar to that present on skeletal muscles does not occur in smooth muscles. Instead, nerve fibers branch diffusely on top of a sheet of smooth muscle fibers without making actual contact. These nerve fibers secrete their neurotransmitter into an interstitial fluid space a few microns from the smooth muscle cells. Two different neurotransmitters, acetylcholine and norepinephrine, are secreted by the

autonomic nervous system nerves that innervate smooth muscles. Acetylcholine is an excitatory neurotransmitter for smooth muscles at some sites and functions as an inhibitory neurotransmitter at other sites. Norepinephrine exerts the reverse effect of acetylcholine.

Uterine Smooth Muscle

Uterine smooth muscle is characterized by a high degree of spontaneous electrical and contractile activity. Unlike the heart, there is no pacemaker, and the contraction process spreads from one cell to another at a rate of 1 to 3 cm/s. Contractions of labor result in peak intrauterine pressures of 60 to 80 mm Hg in the second stage. Resting uterine pressure during labor is approximately 10 mm Hg. Movement of sodium ions appears to be the primary determinant in depolarization, whereas calcium ions are necessary for excitation-contraction coupling. Availability of calcium ions greatly influences the response of uterine smooth muscle to physiologic and pharmacologic stimulation or inhibition. α Excitatory and β inhibitory receptors are also present in the myometrium.

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Neuromuscular-Blocking Drugs and Reversal Agents

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The first successful administration of curare, a neuromuscular-blocking drug (NMBD) to produce surgical relaxation in an anesthetized patient, was reported in 1912, when Arthur Läwen, a German surgeon from Leipzig, used a partially purified preparation of the substance.¹ Läwen's findings were subsequently ignored for nearly three decades until January 23, 1942, when Enid Johnson, following Harold Griffith's instructions, administered 5 mL of curare intravenously to a 20-year-old man who had been anesthetized with cyclopropane via a facemask for an appendectomy. The use of NMBDs in clinical anesthesia has increased exponentially since that time.

The NMBDs that are currently available for clinical use are classified as (1) **depolarizing** NMBDs or (2) **nondepolarizing** NMBDs (**Table 12.1**). Nondepolarizing NMBDs compete with acetylcholine for the active binding sites at the postsynaptic nicotinic acetylcholine receptor and are also called competitive antagonists. Depolarizing NMBDs act as agonists (ie, they are similar in structure to acetylcholine) at postsynaptic nicotinic acetylcholine receptors and cause prolonged membrane depolarization resulting in neuromuscular blockade. Succinylcholine is the only depolarizing NMBD currently in clinical use.

TABLE 12.1

Classification of commonly used and new nondepolarizing neuromuscular-blocking drugs according to duration of action (time to T₁ = 25% of control) after administration of 2 times ED₉₅^{a,b}

	Duration of action		
	Long (>50 min)	Intermediate (20-50 min)	Short (10-20 min)
Steroidal compounds	Pancuronium	Vecuronium Rocuronium	—
Benzylisoquinolinium compounds	Tubocurarine	Atracurium Cisatracurium	Mivacurium

^aED₉₅ is the dose that results in 95% depression of twitch height.

^bThe majority of nondepolarizing neuromuscular-blocking drugs are bisquaternary ammonium compounds. Tubocurarine, vecuronium, and rocuronium are monoquaternary compounds.

Principles of Action of Neuromuscular-Blocking Drugs at the Neuromuscular Junction

In the resting state, the ion channel of the acetylcholine receptor is closed. Simultaneous binding of two acetylcholine molecules to the α subunits initiates conformational changes that open the channel. On the other hand, binding of a single molecule of a nondepolarizing NMBD (a competitive antagonist) to one α subunit is sufficient to produce neuromuscular block (see [Chapter 11](#)).

Succinylcholine produces prolonged depolarization of the endplate region that results in desensitization of nicotinic acetylcholine receptors, inactivation of voltage-gated sodium channels at the neuromuscular junction, and increases in potassium permeability in the surrounding membrane. These electrophysiologic changes will result in membrane hyperpolarization, inhibition of action potential generation, and neuromuscular transmission blockade.

With respect to neuromuscular pharmacology, two enzymes of importance are known to hydrolyze choline esters: acetylcholinesterase and butyrylcholinesterase. Acetylcholinesterase (similar to red cell cholinesterase and also known as "true" cholinesterase) is present at the neuromuscular junction and is

responsible for the rapid hydrolysis of released acetylcholine to acetic acid and choline. Butyrylcholinesterase (also known as plasma cholinesterase or pseudocholinesterase) is synthesized in the liver. Butyrylcholinesterase catalyzes the hydrolysis of succinylcholine, which occurs mainly in the plasma. Plasma cholinesterase also metabolizes mivacurium, cocaine, procaine, and chloroprocaine.

Pharmacology of Succinylcholine

Succinylcholine is the only depolarizing NMBD in clinical use. This compound is also called suxamethonium. Depolarizing block (also called phase I block) is often preceded by muscle fasciculation. The clinical presentation of fasciculations noted after succinylcholine administration is variable (in location and severity) among patients.² The most plausible explanation of succinylcholine-induced fasciculations is that it results from antidromic (retrograde) conduction of action potentials that can activate unparalyzed parts of the motor unit.³ The administration of a small dose of nondepolarizing neuromuscular blocker (precurarization) to prevent a succinylcholine-induced side effects, such as an increase in intraocular pressure, has not been consistently proven in different studies.

Structure-Activity Relationships for Succinylcholine

Succinylcholine is a long, thin, flexible molecule composed of two molecules of acetylcholine linked through the acetate methyl groups. Like acetylcholine, succinylcholine stimulates cholinergic receptors at the neuromuscular junction and at nicotinic (ganglionic) and muscarinic autonomic sites (resulting in side effects that include increased intraocular pressure and intragastric pressure), opening the ionic channel in the acetylcholine receptor, resulting, for example, in cardiac arrhythmias.

Pharmacokinetics, Pharmacodynamics, and Pharmacogenomics of Succinylcholine

Succinylcholine has an elimination half-life of 47 seconds.⁴ The elimination of succinylcholine appears to follow first-order kinetics.^{4,5} The $t_{1/2}$, k_{e0} and Hill coefficient (after fitting two doses of 1 mg/kg succinylcholine) were 244 seconds (standard deviation 157) and 7.9 (standard deviation 3.3), respectively.⁴ The dose of succinylcholine causing on average 95% suppression of twitch height (the ED₉₅) is approximately 0.3 mg/kg.^{6,7}

The usual dose of succinylcholine required for tracheal intubation in adults is 1.0 mg/kg. Administration of succinylcholine 1 mg/kg (3 times the ED₉₅) results in complete suppression of response to neuromuscular stimulation in approximately 60 seconds. In patients with genotypically normal butyrylcholinesterase activity, time to recovery to 90% muscle strength following administration of 1 mg/kg succinylcholine ranges from 9 to 13 minutes.^{8,9} In one study, administration of 0.6 mg/kg of succinylcholine resulted in acceptable intubating conditions at 60 seconds in 95% of patients.¹⁰ The reported proportions of patients with acceptable intubating conditions after administration of 1.0 mg/kg succinylcholine vary from 91.8% to 97%.^{11–13} It also appears that there are no advantages to using succinylcholine doses larger than 1.5 mg/kg in a rapid sequence induction of anesthesia. Paradoxically, succinylcholine doses as large as 2.0 mg/kg (6 times the ED₉₅) guaranteed excellent intubating conditions at 60 seconds in only 86.7% of patients.¹⁴ There is no dose of succinylcholine that can assure 90% excellent conditions in 60 seconds. It should be noted that the adequacy of intubating conditions is related not only to the use of an NMBD but also to the depth of anesthesia, airway anatomy, and the experience of the anesthesiologist.

The short duration of action of succinylcholine is due to its rapid hydrolysis by butyrylcholinesterase (plasma cholinesterase) to succinylmonocholine and choline, such that only 10% of the administered drug reaches the neuromuscular junction. Succinylmonocholine, a metabolite of succinylcholine, is a much weaker neuromuscular-blocking agent than succinylcholine and is metabolized much more slowly to succinic acid and choline.

There is little or no butyrylcholinesterase at the neuromuscular junction. Butyrylcholinesterase influences the onset and duration of action of succinylcholine by controlling the rate at which the drug is hydrolyzed in the plasma before it reaches, and after it leaves, the neuromuscular junction. Recovery from

succinylcholine-induced blockade occurs as succinylcholine diffuses away from the neuromuscular junction, down a concentration gradient as the plasma concentration decreases.

Factors Affecting Butyrylcholinesterase Activity

Butyrylcholinesterase is synthesized by the liver and found in the plasma. The elimination half-time of plasma cholinesterase is 8 to 16 hours, and levels of <75% are necessary for prolongation of succinylcholine effect. Butyrylcholinesterase is responsible for metabolism of succinylcholine, mivacurium, procaine, chloroprocaine, tetracaine, cocaine, and heroin. Neuromuscular block induced by succinylcholine or mivacurium is prolonged when there is a significant reduction in the concentration or activity of butyrylcholinesterase. The activity of the enzyme refers to the number of substrate molecules (μmol) hydrolyzed per unit of time, often expressed in international units.

Factors that have been described as lowering butyrylcholinesterase activity are advanced liver disease, advanced age, malnutrition, pregnancy, burns, oral contraceptives, monoamine oxidase inhibitors, echothiophate, cytotoxic drugs, neoplastic disease, anticholinesterase drugs, metoclopramide, and bambuterol. The β -blocker esmolol inhibits butyrylcholinesterase but causes only a minor prolongation of succinylcholine block. In severe liver disease, plasma cholinesterase activity is reduced to 20% of normal resulting in an increase of duration of apnea after the administration of succinylcholine from a normal duration of 3 minutes to only 9 minutes. When glaucoma is treated with echothiophate, plasma cholinesterase activity was noted to decrease from 49% of control to no activity. The increase in duration of succinylcholine-induced neuromuscular blockade was noted but in no patient did the total duration exceed to 23 minutes.¹⁵

Neostigmine (and to a lesser degree edrophonium) causes a profound decrease in butyrylcholinesterase activity. Even 30 minutes after administration of neostigmine, the butyrylcholinesterase activity remains about 50% of control values. Potent anticholinesterase drugs used in insecticides and occasionally in the treatment of glaucoma and myasthenia gravis, as well as chemotherapeutic drugs (nitrogen mustard and cyclophosphamide), may decrease butyrylcholinesterase activity so that prolonged neuromuscular blockade follows administration of succinylcholine. High estrogen levels, as observed in parturients at term, are associated with up to 40% decreases in butyrylcholinesterase activity. Paradoxically, the duration of action of succinylcholine-induced skeletal muscle paralysis is not prolonged, presumably reflecting an increased volume of distribution of the drug at term.

Genetic Variants of Butyrylcholinesterase

Neuromuscular block induced by succinylcholine or mivacurium can be significantly prolonged if the patient has an abnormal genetic variant of butyrylcholinesterase. Analysis of butyrylcholinesterase involves the determination of both enzyme activity and biochemical phenotypes. Phenotype is determined by the use of specific enzyme inhibitors (such as dibucaine or fluoride) that produce phenotype-specific patterns of dibucaine or fluoride numbers (**Table 12.2**). Molecular genetic analyses can determine the true genotypes.

TABLE 12.2 Relationship between dibucaine number and duration of succinylcholine or mivacurium neuromuscular block				
Type of butyrylcholinesterase	Genotype	Incidence	Dibucaine number ^a	Response to succinylcholine or mivacurium
Homozygous typical	$E_1^uE_1^u$	Normal	70-80	Normal
Heterozygous atypical	$E_1^uE_1^a$	1/480	50-60	Lengthened by 50%-100%
Homozygous atypical	$E_1^aE_1^a$	1/3,200	20-30	Prolonged to 4-8 hours

^aThe dibucaine number indicates the percentage of enzyme inhibited.

Dibucaine, a local anesthetic with an amide linkage, inhibits the activity of normal butyrylcholinesterase by more than 70%, compared with only approximately 20% inhibition of the activity of atypical enzyme. It is important to recognize that the dibucaine number reflects quality of cholinesterase enzyme (ability to

hydrolyze succinylcholine) and not the quantity of the enzyme that is circulating in the plasma. In case of the usual butyrylcholinesterase genotype ($E_1^uE_1^u$), the dibucaine number is 70 or higher, whereas in individuals homozygous for the atypical gene ($E_1^aE_1^a$) (frequency in general population of 1 in 3,500), the dibucaine number is less than 30. In individuals with the heterozygous atypical variant ($E_1^uE_1^a$) (frequency in general population of 1 in 480), the dibucaine number is in the range of 40 to 60.^{16,17} In individuals with the homozygous atypical genotype ($E_1^aE_1^a$), the neuromuscular block induced by succinylcholine or mivacurium is prolonged to 4 to 8 hours, and in individuals with the heterozygous atypical genotype ($E_1^uE_1^a$), the period of neuromuscular block induced by succinylcholine or mivacurium is about 1.5 to 2 times that seen in individuals with the usual genotype ($E_1^uE_1^u$). For a recent review, please see Delacour et al.¹⁸ The longest period of apnea after the administration of succinylcholine was found in patients homozygous for the silent gene ($E_1^sE_1^s$). In those patients, train-of-four (TOF) stimulation will help in detecting the development of phase II block. The decision whether to attempt antagonism of a phase II block has always been controversial, and the use edrophonium or neostigmine do not consistently result in adequate antagonism of neuromuscular blockade.¹⁹ The alternative is to keep the patient adequately sedated and maintain artificial ventilation until the train-of-four ratio (TOFR) has recovered to 0.9 or more.

Fluoride-resistant butyrylcholinesterase variants have also been described. In case of the usual butyrylcholinesterase genotype ($E_1^uE_1^u$), the fluoride number is 60, whereas in individuals with the homozygous atypical genotype ($E_1^fE_1^f$), the fluoride number is 36.²⁰ Individuals with homozygous fluoride-resistant genotype exhibit mild to moderate prolongation of succinylcholine-induced paralysis. The heterozygous fluoride-resistant genotype usually produces clinically insignificant prolongation of succinylcholine block, unless accompanied by a second abnormal allele or by a coexisting acquired cause of butyrylcholinesterase deficiency.

Although the dibucaine or fluoride number indicates the genetic makeup of an individual with respect to butyrylcholinesterase, it does not measure the concentration of the enzyme in the plasma, nor does it indicate the efficiency of the enzyme in hydrolyzing succinylcholine or mivacurium. Both of these latter factors are determined by measuring butyrylcholinesterase activity—which may be influenced by genotype.

Some rare butyrylcholinesterase variants are associated with increased enzyme activity (2-3 times normal).²¹ Resistance to succinylcholine²² and mivacurium²³ as a result of increased butyrylcholinesterase activity has been described.

Side Effects of Succinylcholine

Cardiovascular Effects

Sinus bradycardia, junctional rhythm, and even sinus arrest may follow administration of succinylcholine. These cardiac effects reflect the actions of succinylcholine at cardiac muscarinic cholinergic receptors where the drug mimics the physiologic effects of acetylcholine. Cardiac dysrhythmias are most likely to occur when a second dose of succinylcholine is administered approximately 5 minutes after the first dose. Sinus bradycardia (resulting from stimulation of cardiac muscarinic receptors) is frequently seen in children²⁴ and in adults after a repeated dose of succinylcholine.²⁵ Atropine is effective in treating or preventing bradycardia.

In contrast to actions at cardiac muscarinic cholinergic receptors, the effects of succinylcholine at autonomic nervous system ganglia may produce ganglionic stimulation and associated increases in heart rate and systemic blood pressure. The ganglionic stimulation reflects an effect of succinylcholine on autonomic ganglia that resembles the physiologic effect of acetylcholine at these sites. Ventricular dysrhythmias after succinylcholine administration have been attributed to autonomic stimuli associated with laryngoscopy and tracheal intubation.²⁶

Hyperkalemia

The administration of succinylcholine is associated with approximately 0.5 mEq/dL increase in the plasma potassium concentration in healthy individuals, which is well tolerated and generally does not cause dysrhythmias. Patients with renal failure are no more susceptible to an exaggerated hyperkalemic response to succinylcholine than patients with normal renal function.^{27,28}

Succinylcholine has been associated with severe hyperkalemia in patients with burn, severe abdominal infections,²⁹ severe metabolic acidosis,³⁰ closed head injury,³¹ or conditions associated with upregulation of extrajunctional acetylcholine receptors (eg, hemiplegia or paraplegia, muscular dystrophies, Guillain-Barré syndrome, and burn). For reviews, see Naguib et al³² and Martyn and Richtsfeld.³³ Because of the risk of massive rhabdomyolysis, hyperkalemia, and death in children with undiagnosed muscle disease, succinylcholine is not recommended for use in children except for emergency tracheal intubation.³⁴⁻³⁶

Myoglobinuria

Damage to skeletal muscles is suggested by the occurrence of myoglobinuria after administration of succinylcholine, especially to pediatric patients.³⁷ It is unlikely that succinylcholine-induced fasciculations could produce muscle damage resulting in myoglobinuria.

Most of the patients with rhabdomyolysis and myoglobinuria were subsequently found to have malignant hyperthermia or occult muscular dystrophy.

Increased Intraocular Pressure

Succinylcholine usually causes an increase in intraocular pressure. The intraocular pressure peaks at 2 to 4 minutes after administration and returns to normal by 6 minutes.³⁸ This increase is likely the result of contraction of tonic myofibrils and/or transient dilatation of choroidal blood vessels. The use of succinylcholine is not widely accepted in open eye injury (when the anterior chamber is open) even though succinylcholine was shown to cause no adverse events in a series of 73 patients with penetrating eye injuries.³⁹ The efficacy of precurarization in attenuating increases in intraocular pressure following succinylcholine administration is controversial.⁴⁰⁻⁴²

Increased Intragastric Pressure

Administration of succinylcholine is associated with a variable increase in intragastric and lower esophageal sphincter pressures. The increase in intragastric pressure appears to be related to (1) the intensity of fasciculations of the abdominal skeletal muscles,⁴³ which could be prevented by prior administration of a nondepolarizing NMBD and (2) a direct increase in vagal tone. Administration of succinylcholine does not predispose to regurgitation in patients with an intact lower esophageal sphincter because the increase in intragastric pressure does not exceed the “barrier pressure.”⁴⁴

Increased Intracranial Pressure

Succinylcholine has the potential to increase intracranial pressure. This increase can be attenuated or prevented by pretreatment with a nondepolarizing NMBD.

Myalgias

Postoperative skeletal muscle myalgia, which is particularly prominent in the skeletal muscles of the neck, back, and abdomen, can occur after administration of succinylcholine, especially to young adults undergoing minor surgical procedures that permit early ambulation. Myalgia localized to neck muscles may be perceived as a pharyngitis (“sore throat”) by the patient and attributed to tracheal intubation by the anesthesiologist. Muscle pain occurs more frequently in patients undergoing ambulatory surgery, especially in women, than in bedridden patients.⁴⁵ The incidence of muscle pain following administration of succinylcholine varies from 0.2% to 89%.⁴⁶ The mechanism of succinylcholine-induced myalgia appears to be complex and is not fully understood. One hypothesis proposes that myalgia is secondary to muscle damage by succinylcholine-induced fasciculations.⁴⁵ This hypothesis is supported by findings of myoglobinemia and increases in serum creatine kinase level following succinylcholine administration.^{37,47,48} However, although prior administration

of a small dose of a nondepolarizing NMBD prevents fasciculations due to succinylcholine, this approach is not always effective in preventing succinylcholine-induced myalgia.⁴⁶⁻⁴⁹ Another hypothesis suggests a possible role for prostaglandins and cyclooxygenases in succinylcholine-induced myalgias.^{2,50} Pretreatment with a prostaglandin inhibitor (lysine acetyl salicylate or diclofenac) has been shown to be effective in decreasing the incidence of muscle pain after succinylcholine administration.^{2,51} A meta-analysis showed that myalgia may best be prevented with muscle relaxants, lidocaine, or nonsteroidal antiinflammatory drugs.⁵² It should be noted, however, that myalgias following outpatient surgery occur even in the absence of succinylcholine.^{53,54}

Masseter Spasm

Succinylcholine is a known trigger agent for malignant hyperthermia. Although an increase in tone of the masseter muscle may be an early indicator of malignant hyperthermia,⁵⁵ it is not consistently associated with malignant hyperthermia.⁵⁶⁻⁵⁸ It has been suggested that the high incidence of masseter spasm in children given succinylcholine may be due to inadequate succinylcholine dosage.⁵⁹

Pharmacology of Nondepolarizing Neuromuscular-Blocking Drugs

Nondepolarizing NMBDs act as competitive antagonists by binding to the α subunits of the nicotinic acetylcholine receptor. The NMBDs have been classically classified either based on their chemical class (the steroid, benzylisoquinolinium, and other NMBDs) or based on the duration of action (long acting, intermediate acting, or short acting) of equipotent doses (see **Table 12.1**). Nondepolarizing NMBDs are positively charged, relatively large molecules. In general, a dose of 2 to 3 times ED₉₅ is used to facilitate tracheal intubation, whereas a dose of 10% of the ED₉₅ is used to maintain neuromuscular blockade.

Benzylisoquinolinium Compounds

The South American Indians' arrow poisons, known as curare, served as the basis for the development of the benzylisoquinoline-type relaxants. Tubocurarine was introduced as an NMBD for use during surgical anesthesia, but it is not currently in use anymore because of its side effects.^{1,60}

Atracurium

Atracurium consists of a racemic mixture of 10 stereoisomers.^{61,62} These isomers have been separated into three geometrical isomer groups that are designated *cis-cis*, *cis-trans*, and *trans-trans* based on their configuration about the tetrahydroisoquinoline ring system.^{61,62} The ratio of the *cis-cis*, *cis-trans*, and *trans-trans* isomers is approximately 10:6:1.⁶³

Atracurium has been designed to undergo spontaneous degradation at physiologic temperature and pH by a mechanism called Hofmann elimination, yielding laudanosine (a tertiary amine) and a monoquaternary acrylate as metabolites.^{61,64} Furthermore, atracurium can undergo ester hydrolysis. Hofmann elimination is a purely chemical process that results in loss of the positive charges by molecular fragmentation to laudanosine and a monoquaternary acrylate.^{65,66} Laudanosine depends on the liver for clearance, with approximately 70% excreted in the bile and the remainder in urine.⁶⁷ Hepatic cirrhosis in humans does not alter clearance of laudanosine, whereas excretion of this metabolite is impaired in patients with biliary obstruction.⁶⁸ Laudanosine easily crosses the blood–brain barrier, and it has central nervous system stimulating properties. The seizure threshold is not known in humans. In patients in the intensive care unit, blood levels of laudanosine can be as high as 5.0 to 6.0 $\mu\text{g}/\text{mL}$.⁶⁹ There is no evidence to suggest that prolonged administration of atracurium in the operating room or in the intensive care unit in patients with normal or impaired renal function is likely to result in concentrations of laudanosine capable of producing convulsions. The plasma elimination half-life of laudanosine is similar in patients with normal and impaired renal function — 197 \pm 38 and 234 \pm 81 minutes, respectively.^{70,71}

Cisatracurium

Cisatracurium is the 1R *cis*-1'R *cis* isomer of atracurium and represents about 15% of the marketed atracurium mixture by weight but more than 50% of the mixture in terms of potency or neuromuscular-blocking activity. Like atracurium, cisatracurium is metabolized by Hofmann elimination to laudanosine and a monoquaternary alcohol metabolite.⁷²⁻⁷⁴ There is no ester hydrolysis of the parent molecule.⁷² Hofmann elimination accounts for 77% of the total clearance of 5 to 6 mL/kg/min.⁷⁵ Twenty-three percent of the drug is cleared through organ-dependent means, with renal elimination accounting for 16% of this.⁷⁴ Because cisatracurium is about 4 to 5 times as potent as atracurium, about 5 times less laudanosine is produced, and accumulation of this metabolite is not thought to be of any consequence in clinical practice. Unlike atracurium, cisatracurium in the clinical dose range does not cause histamine release.^{76,77} This indicates that the phenomenon of histamine release may be stereospecific.^{76,78}

Mivacurium

Mivacurium consists of a mixture of three stereoisomers. Mivacurium is metabolized by butyrylcholinesterase at about 70% to 88% rate of succinylcholine to a monoester, a dicarboxylic acid.^{79,80} Mivacurium may produce histamine release, especially if administered rapidly.⁸¹

Steroidal Compounds

The steroid skeleton possesses onium centers at different positions. In the steroidal compounds, it is probably essential that one of two nitrogen atoms in the molecule be quaternized.⁸² The presence of acetyl ester (acetylcholine-like moiety) is thought to facilitate interaction of steroidal compounds with nicotinic acetylcholine receptors at the postsynaptic muscle membrane.^{83,84}

Pancuronium

Pancuronium is a potent long-acting NMBD with vagolytic, direct sympathomimetic stimulation because it blocks the reuptake of norepinephrine and butyrylcholinesterase-inhibiting properties.⁸⁵ About 40% to 60% of pancuronium is cleared by the kidney,⁸⁶ and 11% is excreted in the bile. A small amount (15%-20%) is metabolized, mainly by deacetylation in the liver. The metabolites (3-OH, 17-OH, and 3,7-di-OH) are considerably less potent as NMBDs and are excreted in the urine.⁸⁷ Accumulation of the 3-OH metabolite is responsible for prolongation of the duration of block induced by pancuronium. Given its prolonged effect and the concern for postoperative residual paralysis and associated morbidity, many clinicians elect to use other NMBD when trying to achieve neuromuscular blockade in their patients.

Vecuronium

Vecuronium is a monoquaternary NMBD with an intermediate duration of action. Vecuronium is simply pancuronium without the quaternizing methyl group in the 2-piperidino substitution. The minor molecular difference between vecuronium and pancuronium means that vecuronium is characterized by (1) a slight decrease in potency; (2) virtual loss of the vagolytic properties of pancuronium; (3) molecular instability in solution (this explains in part the shorter duration of action of vecuronium compared with pancuronium); and (4) increased lipid solubility, which results in a greater biliary elimination of vecuronium than pancuronium.

The liver is the principal organ of elimination for vecuronium, and renal excretion accounts for excretion of approximately 30% of the administered dose. Approximately 30% to 40% of vecuronium is cleared in the bile as parent compound.⁸⁸ The duration of the vecuronium-induced neuromuscular block is therefore dependent primarily on hepatic function and, to a lesser extent, on renal function.^{89,90} Vecuronium is metabolized in the liver by deacetylation into three possible metabolites: 3-OH, 17-OH, and 3,17-di-OH vecuronium. The 3-OH metabolite has 80% the neuromuscular-blocking potency of vecuronium. Therefore, during prolonged administration of vecuronium, this metabolite may contribute to prolonged neuromuscular blockade.⁹¹

Vecuronium is prepared as a lyophilized powder because it is less stable in solution. Vecuronium cannot be prepared as a ready-to-use solution with a sufficient shelf life, even as a buffered solution.⁹² In

pancuronium, the 2-piperidine is quaternized and no longer basic (charged). Thus, it does not participate in catalysis of the 3-acetate hydrolysis.

Rocuronium

Rocuronium is an intermediate-acting monoquaternary NMBD with a faster onset of action than either pancuronium or vecuronium. Rocuronium is about 6 times less potent than vecuronium.^{93,94} Rocuronium is primarily eliminated by the liver and excreted in bile. It is taken up into the liver by a carrier-mediated active transport system. The putative metabolite, 17-desacetylrocuronium, has not been detected in significant quantities. Approximately 30% of rocuronium is excreted unchanged in the urine. At room temperature, rocuronium is stable for 60 days, whereas pancuronium is stable for 6 months.

Potency of Nondepolarizing Neuromuscular-Blocking Drugs

Drug potency is commonly expressed in terms of the dose-response relationship. The potency of nondepolarizing NMBDs can be expressed as the dose of drug required to produce an effect—for example, 50% or 95% depression of twitch height, commonly expressed as ED₅₀ and ED₉₅, respectively.

Effect of Drug Potency on Speed of Onset

The speed of onset of action is inversely proportional to the potency of nondepolarizing NMBDs. Low potency is predictive of rapid onset, and high potency is predictive of slow onset. Except for atracurium,⁹⁵ molar potency (the ED₅₀ or ED₉₅ expressed in μM/kg) is highly predictive of a drug's time to onset of effect (at the adductor pollicis muscle).⁹⁶ Rocuronium has a molar potency (ED₉₅ ≈ 0.54 μM/kg), which is about 13% that of vecuronium and only 9% that of cisatracurium. Thus, rapid onset of rocuronium is to be expected.

The influence of potency on speed of onset could be simply explained by the fact that, for an equipotent dose (eg, a dose that results in 50% receptor occupancy), a low-potency drug (such as rocuronium) will have a higher number of molecules than a high-potency drug (such as tubocurarine). The higher number of drug molecules will result in a greater diffusion gradient of the low-potency drug from capillary to the neuromuscular junction (faster rate of drug transfer from plasma to biophase) and a greater biophase concentration of low-potency drug resulting in a fast onset.

The concept of “buffered diffusion” must be invoked to explain the slow recovery of long-acting NMBDs and to understand biophase kinetics.⁹⁷ Buffered diffusion is the process in which diffusion of a drug (eg, diffusion of an NMBD from the neuromuscular junction) is impeded because it binds to extremely high-density receptors within a restricted space (neuromuscular junction). This process is seen with high-potency but not low-potency drugs. Buffered diffusion causes repetitive binding to and unbinding from receptors, keeping potent drugs such as tubocurarine in the neighborhood of effector sites and potentially lengthening the duration of effect.

Factors That Increase the Potency of Nondepolarizing Neuromuscular-Blocking Drugs

Inhalational anesthetics potentiate the neuromuscular-blocking effect of nondepolarizing NMBDs. This potentiation results mainly in a decrease in the required dosage of nondepolarizing NMBD and prolongation of both the duration of action of the relaxant and recovery from neuromuscular block. The magnitude of this potentiation depends on several factors, including the duration of inhalational anesthesia, the specific inhalational anesthetic used,⁹⁸ and the concentration of inhalational agent used. The rank order of potentiation is desflurane > sevoflurane > isoflurane > halothane > nitrous oxide–barbiturate–opioid or propofol anesthesia. The mechanisms proposed for this potentiation include (1) a central effect on α motoneurons and interneuronal synapses, (2) inhibition of postsynaptic nicotinic acetylcholine receptors, and (3) augmentation of the antagonist’s affinity at the receptor site.

Some antibiotics can also potentiate neuromuscular blockade. The aminoglycoside antibiotics, the polymyxins, and lincomycin and clindamycin primarily inhibit the prejunctional release of acetylcholine and

also depress postjunctional nicotinic acetylcholine receptor sensitivity to acetylcholine. The tetracyclines, on the other hand, exhibit postjunctional activity only.

Hypothermia or magnesium sulfate potentiates the neuromuscular blockade induced by nondepolarizing NMBDs. The recovery to 10% twitch height with 0.1 mg/kg of vecuronium increases from 28 minutes at a mean central temperature of 36.4°C to 64 minutes at 34.4°C.⁹⁹ If the skin temperature is dropped to 27°C, the interpretation of response in that arm is unreliable.¹⁰⁰ The mechanism(s) underlying this potentiation may be pharmacodynamic, pharmacokinetic, or both. High magnesium concentrations inhibit calcium channels at the presynaptic nerve terminals that trigger the release of acetylcholine.

Most local anesthetics when given in large doses potentiate neuromuscular block; in smaller doses, no clinically significant potentiation occurs. Antidysrhythmic drugs, such as quinidine, also potentiate neuromuscular block.

Factors That Decrease the Potency of Nondepolarizing Neuromuscular-Blocking Drugs

Resistance to nondepolarizing NMBDs (except for mivacurium¹⁰¹ and probably atracurium¹⁰²) has been demonstrated in patients receiving chronic anticonvulsant therapy, as evidenced by accelerated recovery from neuromuscular blockade and the need for increased doses to achieve complete neuromuscular blockade.^{102,103} This resistance has been attributed to increased clearance, increased binding of the nondepolarizing NMBDs to α_1 -acid glycoproteins, and/or upregulation of neuromuscular acetylcholine receptors.

In hyperparathyroidism, hypercalcemia is associated with decreased sensitivity to atracurium and thus a shortened duration of neuromuscular blockade. Increasing calcium concentrations also decreased the sensitivity to tubocurarine and pancuronium in a muscle-nerve model.¹⁰⁴

Adverse Effects of Nondepolarizing Neuromuscular-Blocking Drugs

Neuromuscular-blocking agents seem to play a prominent role in adverse reactions that occur during anesthesia. The Committee on Safety of Medicines in the United Kingdom reported that 10.8% (218 of 2,014) of adverse drug reactions and 7.3% of deaths (21 of 286) were attributable to NMBDs.¹⁰⁵

Autonomic Effects

Neuromuscular-blocking agents interact with nicotinic and muscarinic cholinergic receptors within the sympathetic and parasympathetic nervous systems and at the nicotinic receptors of the neuromuscular junction. Administration of tubocurarine was associated with marked ganglion blockade resulting in hypotension; in susceptible patients, manifestations of histamine release such as flushing, hypotension, reflex tachycardia, and bronchospasm can be seen. Pancuronium has a direct vagolytic effect. Pancuronium can block muscarinic receptors on sympathetic postganglionic nerve terminals,¹⁰⁶ resulting in inhibition of a negative-feedback mechanism whereby excessive catecholamine release is modulated or prevented.¹⁰⁷ Pancuronium may also stimulate catecholamine release from adrenergic nerve terminals.¹⁰⁸

Histamine Release

Histamine release by benzylisoquinolinium compounds such as mivacurium, atracurium, and tubocurarine can cause skin flushing, decreases in blood pressure and systemic vascular resistance, and increases in pulse rate.^{81,109–112} In contrast, steroid NMBDs are not associated with histamine release in typical clinical doses.^{113–115} The clinical effects of histamine are seen when plasma concentrations increase to 200% to 300% of baseline values, especially if such concentrations are achieved quickly by rapid drug administration. The effect is usually of short duration (1–5 minutes), is dose related, and is clinically insignificant in healthy patients. Histamine has positive inotropic and chronotropic effects on the myocardial H₂ receptors, and there is some evidence that its chronotropic effect may result in part from the liberation of catecholamines.¹¹⁶ Although ganglionic block secondary to the administration of tubocurarine has been demonstrated to occur in various species,¹¹⁷ the peripheral venous and arteriolar dilatation via stimulation of vascular H₁ and H₂ receptors can result in a significant degree of hypotension as well as carotid-sinus-mediated reflex response to histamine-induced peripheral vasodilatation.¹¹¹ Other substances liberated by mast cell degranulation, such

as tryptase or prostaglandins, may also play a role.¹¹⁸ The serosal mast cell, located in the skin and connective tissue and near blood vessels and nerves, is principally involved in the degranulation process.¹¹⁸

For patients who may be compromised hemodynamically, selecting a drug with less or no histamine release (cisatracurium, vecuronium, or rocuronium) may be appropriate. Another strategy for maintaining cardiovascular stability involves slow administration of benzylisoquinolinium NMBDs (over 60 seconds) or the prophylactic use of the combined histamine H₁- and H₂-receptor antagonists.

The administration of benzylisoquinolinium NMBDs (with the exception of cisatracurium) is associated with histamine release, which may result in increased airway resistance and bronchospasm in patients with hyperactive airway disease.

Allergic Reactions

Life-threatening anaphylactic (immune-mediated) or anaphylactoid reactions during anesthesia have been estimated to occur in 1 in 1,000 to 1 in 25,000 administrations and are associated with a mortality rate of about 5%.^{119,120} In France, the most common causes of anaphylaxis in patients who experienced allergic reactions were reported to be NMBDs (58.2%), latex (16.7%), and antibiotics (15.1%).¹²¹ Anaphylactic reactions are mediated through immune responses involving immunoglobulin E antibodies fixed to mast cells. Anaphylactoid reactions are not immune mediated and represent exaggerated pharmacologic responses in very sensitive individuals, who represent a very small proportion of the population. Cross-reactivity has been reported between NMBDs and food, cosmetics, disinfectants, and industrial materials.

Steroidal compounds (eg, rocuronium, vecuronium, or pancuronium) result in no significant histamine release. Nevertheless, in the aforementioned series from France, among cases of anaphylaxis due to NMBDs, 43.1% were due to rocuronium and 22.6% to succinylcholine.¹²¹ There are currently no standards regarding which diagnostic tests (skin prick test, interdermal test, or immunoglobulin E testing) should be performed to identify patients at risk.¹²²

Treatment of anaphylactic reactions include immediate administration of oxygen (100%) and intravenous epinephrine (10-20 µg/kg). Early tracheal intubation with a cuffed endotracheal tube should be considered in patients with rapidly developing angioedema. Fluids (crystalloid and/or colloid solutions) must be administered concurrently. Norepinephrine or a sympathomimetic drug (eg, phenylephrine) may also be necessary to maintain perfusion pressure until the intravascular fluid volume can be restored. Dysrhythmias should be treated. The use of antihistamines and/or steroids is controversial.

Drugs for Reversal of Nondepolarizing Neuromuscular Blockade

Acetylcholinesterase at the Neuromuscular Junction

At the neuromuscular junction, acetylcholinesterase is enzyme responsible for rapid hydrolysis of released acetylcholine.¹²³ Approximately 50% of the released acetylcholine is hydrolyzed during its diffusion across the synaptic cleft, before reaching nicotinic acetylcholine receptors. Acetylcholinesterase has one of the highest catalytic efficiencies known. It can catalyze acetylcholine hydrolysis at a rate of 4,000 molecules of acetylcholine hydrolyzed per active site per second, which is nearly the rate of diffusion.¹²³

Acetylcholinesterase is highly concentrated at the neuromuscular junction but is present in a lower concentration throughout the length of muscle fibers (see [Chapter 10](#)).¹²⁴

Mechanisms of Action of Acetylcholinesterase Inhibitors

Acetylcholinesterase inhibitors (eg, neostigmine, edrophonium, and less commonly, pyridostigmine) are used clinically to antagonize the residual effects of nondepolarizing NMBDs and to accelerate recovery from nondepolarizing neuromuscular blockade. Acetylcholine accumulates at the neuromuscular junction after administration of neostigmine and competes with the residual molecules of the nondepolarizing NMBD drug for the available unoccupied nicotinic acetylcholine receptors at the neuromuscular junction. The clinical implication is that neostigmine has a ceiling effect on acetylcholinesterase. Once the inhibition of acetylcholinesterase is complete, administering additional doses of neostigmine will serve no useful purpose

because the concentration of acetylcholine that can be produced at the neuromuscular junction is finite. “In practical terms, the maximum depth of block that can be antagonized approximately corresponds to the reappearance of the fourth response to TOF stimulation.”¹²⁵ Because of their ceiling effect, the anticholinesterases cannot effectively antagonize profound or deep levels of neuromuscular blockade.

For neostigmine, the maximum effective dose is in the 60 to 80 µg/kg range, and for edrophonium, it is in the 1.0 to 1.5 mg/kg range. Antagonism of residual neuromuscular blockade induced by the various nondepolarizing NMBDs is similar (or possibly greater) in children and adults.¹²⁶ Neostigmine is still the anticholinesterase agent most widely used by anesthesiologists worldwide.¹²⁷

The notion that neostigmine administration at a time when spontaneous clinical recovery from nondepolarizing block is almost complete may have adverse clinical consequences has been disputed.^{128–132} The effect of an anticholinesterase on neuromuscular transmission seems to be dependent whether or not a nondepolarizing NMBD is present at the neuromuscular junction.^{133,134} When the fade cannot be detected on TOF stimulation at the adductor pollicis muscle using a conventional peripheral nerve stimulator (PNS) following spontaneous recovery from a nondepolarizing NMBD, available evidence suggests that the prudent course of action is to administer a small (≤ 30 µg/kg) dose of neostigmine.

Clinical Pharmacology

Pharmacokinetics of Acetylcholinesterase Inhibitors

The elimination half-life of edrophonium is similar to those of neostigmine and pyridostigmine, although that of pyridostigmine is somewhat longer. Renal excretion accounts for about 50% of the excretion of neostigmine and about 75% of that of pyridostigmine and edrophonium. Renal failure decreases the plasma clearance of neostigmine, pyridostigmine, and edrophonium as much as, if not more than, that of the long-acting nondepolarizing NMBDs.

Side Effects of Acetylcholinesterase Inhibitors

Inhibition of acetylcholinesterase increases the concentration of acetylcholine not only at the neuromuscular junction (nicotinic site) but also at all other synapses that use acetylcholine as a transmitter.

Cardiovascular Side Effects

Because only the nicotinic effects of acetylcholinesterase inhibitors are desired, the muscarinic effects must be blocked by atropine or glycopyrrolate.⁸⁴ To minimize the muscarinic cardiovascular side effects of acetylcholinesterase inhibitors, an anticholinergic agent should be coadministered with the acetylcholinesterase inhibitor. Atropine (7-10 µg/kg) matches the onset of action and pharmacodynamic profile of the rapid-acting edrophonium (0.5-1.0 mg/kg),⁸⁴ and glycopyrrolate (7-15 µg/kg) matches the slower acting neostigmine (40-70 µg/kg) and pyridostigmine.^{135,136} In patients with preexisting cardiac disease, glycopyrrolate may be preferable to atropine,¹³⁷ and the acetylcholinesterase inhibitor and anticholinergic should be administered slowly (eg, over 2-5 minutes). The hemodynamic effects of tracheal extubation are significantly greater than that following the coadministration of neostigmine and glycopyrrolate.

Pulmonary and Alimentary Side Effects

Administration of acetylcholinesterase inhibitors is associated with bronchoconstriction, increased airway resistance, increased salivation, and increased bowel motility (muscarinic effects). Anticholinergics tend to reduce this effect. There is no evidence to indicate that neostigmine increases the incidence of postoperative nausea and vomiting.¹³⁸ Neostigmine has been described as having antiemetic properties and as having no effect on the incidence of postoperative nausea and vomiting.

Limitations of Acetylcholinesterase Inhibitors

As indicated in the previous sections, postanesthetic morbidity in the form of incomplete reversal and residual postoperative weakness is a frequent occurrence.^{139–144} In 2003, for example, Debaene and

colleagues¹⁴⁰ reported a 45% incidence of postoperative residual neuromuscular blockade in patients arriving in the postanesthesia care unit. Moreover, surveys indicated that most practitioners demonstrated overconfidence in their knowledge and ability to manage the use of NMBDs¹⁴⁵ and do not know what constitutes adequate recovery from neuromuscular blockade.¹⁴⁶ Although an argument can be made that these problems could be attributed to (1) lack of routine use of PNSs (and more importantly, the quantitative ones) or (2) the ceiling effect of the reversal agents when administered at a deep level of neuromuscular blockade,^{147,148} one study found that, despite both the use of nerve stimulators by clinicians with knowledge and expertise and administration of neostigmine, the incidence of critical respiratory events in the postoperative care unit remained a significant 0.8%.¹⁴² Clearly, avoidance of critical respiratory events requires changes in clinical care (see [Quantitative vs Qualitative Measurement](#) in the discussion section that follows).¹⁴⁹

Sugammadex: A Selective Relaxant Binding Agent

Chemistry

Cyclodextrins are cyclic dextrose units joined through one to four glycosyl bonds that are produced from starch or starch derivatives using cyclodextrin glycosyltransferase. The three natural unmodified cyclodextrins consist of 6-, 7-, or 8-cyclic oligosaccharides and are called α -, β -, or γ -cyclodextrin, respectively. Their three-dimensional structures, which resemble a hollow, truncated cone or a doughnut, have a hydrophobic cavity and a hydrophilic exterior because of the presence of polar hydroxyl groups.

Sugammadex is a modified γ -cyclodextrin compound composed of an eight-membered ring with a central cavity that encapsulates steroid NMBDs.^{150–153} This modification entails (1) the addition of eight side chains to extend the cavity of γ -cyclodextrin in order to better accommodate the four hydrophobic steroid rings of rocuronium and (2) the inclusion of negatively charged carboxyl groups at the end of the side chains in order to enhance electrostatic binding to the positively charged quaternary nitrogen of rocuronium. Sugammadex exerts its effect by forming very tight complexes at a 1:1 ratio with steroid neuromuscular-blocking agents (rocuronium > vecuronium >> pancuronium) ([Figure 12.1](#)). The intermolecular (van der Waals) forces, thermodynamic (hydrogen) bonds, and hydrophobic interactions of the sugammadex-rocuronium complex make it very tight.¹⁵⁰ The sugammadex-rocuronium complex has a very high association rate and a very low dissociation rate. It is estimated that for every 30 million sugammadex-rocuronium complexes, only one complex dissociates.

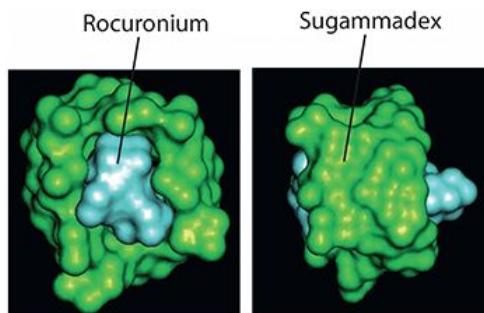


FIGURE 12.1 Encapsulation of rocuronium molecule (blue) by a sugammadex molecule (green) at 1:1 ratio. Reprinted with permission from Naguib M. Sugammadex: another milestone in clinical neuromuscular pharmacology. Anesth Analg. 2007;104(3):575-581. Copyright © 2007 International Anesthesia Research Society.

Sugammadex is the first selective relaxant-binding agent. It exerts no effect on acetylcholinesterases or on any receptor system in the body, thus eliminating the need for anticholinergic drugs and their undesirable adverse effects. Moreover, the unique mechanism of reversal by encapsulation is independent of the depth of neuromuscular block; thus, reversal can be accomplished even during profound neuromuscular block.

Pharmacokinetics

Sugammadex is biologically inactive and does not bind to plasma proteins. Metabolism of sugammadex is at most very limited, and approximately 75% of the dose was eliminated through the urine. The mean percentage of the dose excreted in urine up to 24 hours after administration varied between 59% and 80%. In patients with substantial renal impairment, clearances of sugammadex and rocuronium were decreased by a factor of 16 and 3.7, respectively, relative to that in healthy subjects, and the elimination half-lives were increased by a factor of 15 and 2.5, respectively. The effectiveness of dialysis in removing sugammadex and rocuronium from plasma was not demonstrated consistently. Therefore, sugammadex should be avoided in patients with a creatinine clearance of <30 mL/min. The main reason for not recommending sugammadex in this population because of the lack of safety data on the ultimate disposition of this complex in humans with end-stage renal disease. It is likely that sugammadex-rocuronium complex will be deposited in the reticuloendothelial system in the body.

In the absence of sugammadex, rocuronium is eliminated mainly by biliary excretion (>75%) and to a lesser degree by renal excretion (10%-25%). The plasma clearance of sugammadex alone is approximately 3 times lower than that of rocuronium alone. In volunteers, the plasma clearance of rocuronium was decreased by a factor of >2 after administration of a ≥ 2.0 mg/kg dose of sugammadex. This is because the biliary route of excretion becomes unavailable for the rocuronium-sugammadex complex, and rocuronium clearance decreases to a value approaching the glomerular filtration rate (120 mL/minute). As noted earlier, after administration of sugammadex, the plasma concentration of free rocuronium decreases rapidly, but the total plasma concentration of rocuronium (both free and that bound to sugammadex) increases.

Pharmacodynamics

Sugammadex, used in appropriate doses, is capable of reversing any depth of neuromuscular blockade (profound or shallow) induced by rocuronium or vecuronium to a TOFR of ≥ 0.9 within 3 minutes.^{144,154} During rocuronium- or vecuronium-induced neuromuscular blockade, intravenous administration of sugammadex results in rapid removal of free rocuronium or vecuronium molecules from the plasma. This creates a concentration gradient favoring movement of the remaining rocuronium or vecuronium molecules from the neuromuscular junction back into the plasma, where they are encapsulated by free sugammadex molecules. The latter molecules also enter the tissues and form a complex with the rocuronium or vecuronium. Therefore, the neuromuscular blockade of these agents is terminated rapidly by their diffusion away from the neuromuscular junction back into the plasma. This results in an increase in the total plasma concentration of rocuronium (both free and bound to sugammadex)¹⁵⁵ or vecuronium.

At doses of 2 mg/kg, sugammadex reverses rocuronium and vecuronium when the TOF count is at least 2 in about 3 minutes. A dose of 4 mg/kg is recommended for antagonism of deeper levels of blockade (such as when only posttetanic twitches are present). A dose of 16 mg/kg can be used to rapidly and emergently reverse the effects of 1.2 mg/kg rocuronium. This dose of sugammadex restores muscle function faster than the spontaneous recovery from succinylcholine administration ([Figure 12.2](#)). However, pharmacologic intervention with sugammadex should not be relied on to rescue patients in the setting of “cannot intubate, cannot ventilate” (CICV) situation ([Figure 12.3](#)). Following induction of anesthesia, rescue reversal of 1.2 mg/kg rocuronium with 16 mg/kg sugammadex in the setting of CICV may still not result in reliable, immediate return of spontaneous ventilation. In a simulation study, it was reported that, in obese and morbidly obese patients, even after adequate preoxygenation, neuromuscular reversal may not be sufficiently rapid to prevent significant hemoglobin desaturation. The clinical management of CICV should primarily focus on restoration of airway patency, oxygenation, and ventilation consistent with the American Society of Anesthesiologist’s Practice guidelines for management of the difficult airway.¹⁵⁶

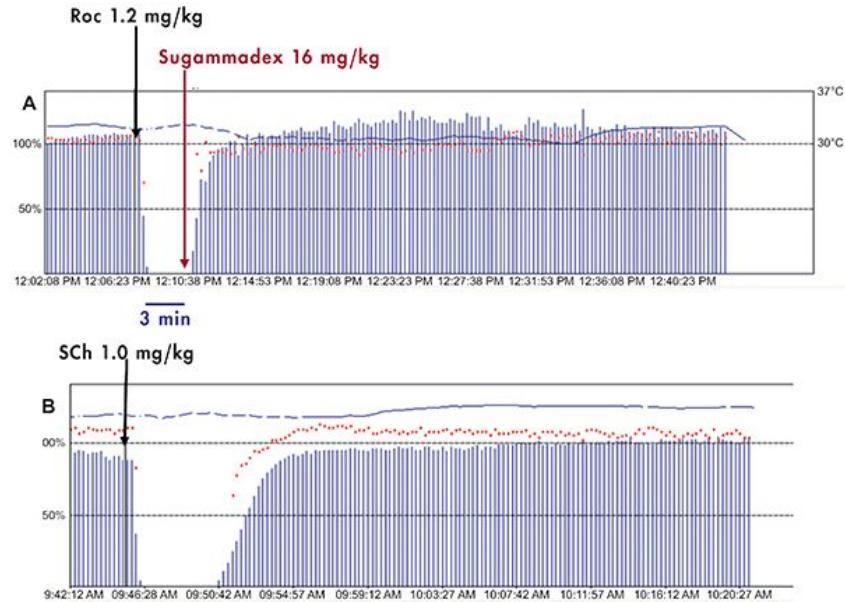


FIGURE 12.2 Panel A shows the recovery of the twitch height and train-of-four (TOF) ratio after administration of 1.2 mg/kg rocuronium (Roc) followed 3 minutes later by 16 mg/kg sugammadex, both given intravenously. Recovery to a first twitch height (T1) of 90% and a TOF ratio of 0.94 occurred 110 second later. The onset-offset time with this sequence (ie, the time from the end of the injection of rocuronium to a T1 recovery to 90%) was 4 min 47 s. Panel B shows the effects of administering 1.0 mg/kg succinylcholine (SCh) with spontaneous recovery to a T1 of 90% occurring after 9 minutes and 23 seconds. *Reprinted with permission from Naguib M. Sugammadex: another milestone in clinical neuromuscular pharmacology. Anesth Analg. 2007;104(3):575-581. Copyright © 2007 International Anesthesia Research Society.*

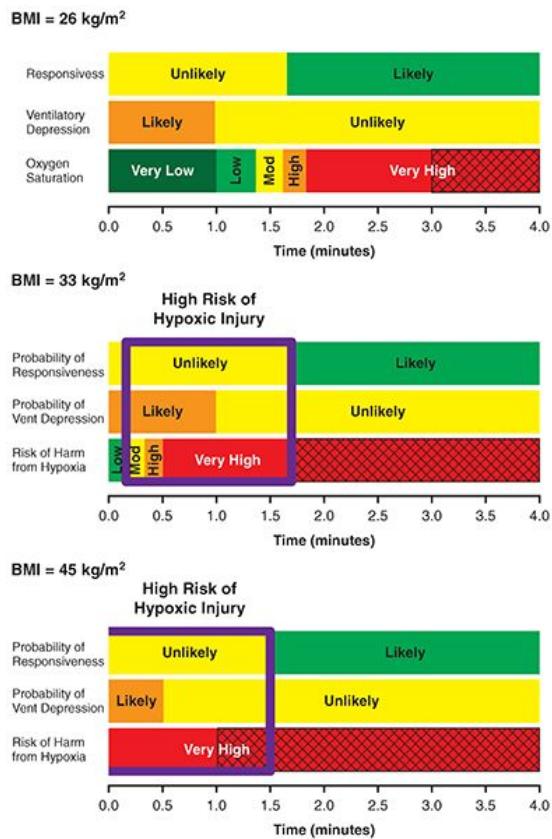


FIGURE 12.3 Comparison of responsiveness, intolerable ventilatory depression (a respiratory rate of ≤ 4 breaths/min), and hypoxia to estimate periods of *high risk of hypoxic injury* after induction with failure to ventilate or secure the airway. For discussion purposes, the duration of effects presented in this table is presented as the time from reversal of rocuronium neuromuscular blockade with sugammadex until selected endpoints in drug effects. See methods for criteria used to estimate a high risk of hypoxic injury. [Figure 12.2](#), upper and middle panels present the definitions of the scales used to characterize the probability of effects. Time segments that met criteria are identified with a blue rectangle. The purple rectangle for the body mass index (BMI) of 45 kg/m^2 is truncated at time = 0 min because criteria were met for a high risk of injury 1.5 minute before reversal with sugammadex. *Reprinted with permission from Naguib M, Brewer L, LaPierre C, et al. The Myth of Rescue Reversal in “Can’t Intubate, Can’t Ventilate” Scenarios. Anesth Analg. 2016;123(1):82-92. Copyright © 2016 International Anesthesia Research Society.*

Sugammadex is ineffective against succinylcholine and benzylisoquinolinium NMBDs such as mivacurium, atracurium, and cisatracurium because it cannot form inclusion complexes with these drugs.¹⁵⁷ For example, the association rate constant, which reflects the binding affinity for sugammadex, is 1.79×10^7 for rocuronium and 3.79×10^3 for atracurium.¹⁵⁸ This means that sugammadex affinity for rocuronium is 4,723 times that of atracurium. In fact, in anesthetized rhesus monkey, the speed of recovery following 1 mg/kg of sugammadex was not different from spontaneous recovery during atracurium-induced neuromuscular block.¹⁵⁷ Therefore, if neuromuscular blockade must be reestablished after using sugammadex, one of the benzylisoquinolinium NMBDs should be considered.

Drug Interactions

Sugammadex can bind and inhibit oral contraceptives. Patients should use alternative contraceptive techniques for 7 days after exposure to sugammadex.¹⁵⁸

Adverse Effects

The use of sugammadex may cause anaphylactic reaction. A recent retrospective analysis from Japan suggested that the incidence of anaphylaxis to sugammadex is approximately 0.04% of administrations, which would be comparable with that encountered with rocuronium.¹⁵⁹ Tryptase plasma concentrations must be estimated during the acute event and repeated about 2 to 6 hours later to have an accurate indication of an anaphylactic response. Ideally, a third sample should be taken at 24 hours when the plasma tryptase levels would be expected to have returned to normal values.¹⁶⁰

Cardiac arrhythmias, including marked bradycardia and asystole, may occur after administration of sugammadex.¹⁶⁰ Thus, full electrocardiogram monitoring should be continued during and after administration of sugammadex, and atropine and other vasoactive drugs should be immediately available.¹⁶⁰ From 2009 to 2017, 138 cases of serious cardiac adverse events with nine deaths after administration of sugammadex were reported to the US Food and Drug Administration adverse events reporting system, including bradycardia ($n = 66$), cardiac arrest ($n = 39$), ventricular fibrillation ($n = 10$), and ventricular tachycardia ($n = 8$).¹⁶¹ Although sugammadex-induced bradycardia is typically transient, it has precipitated cardiac arrest and hemodynamic collapse in some cases.¹⁶²

Small increases in activated partial thromboplastin time and prothrombin time have been reported after sugammadex administration, but clinically significant bleeding has not been reported.¹⁶³

Monitoring of Neuromuscular Function

Monitoring of neuromuscular function after administration of an NMBD serves at least two purposes in clinical settings. First, it allows the anesthesiologist to administer these agents with appropriate dosing; second, it ensures that the patient recovers adequately from residual effects of the NMBD (ie, TOFR ≥ 0.90), thus guaranteeing patient safety. Residual postoperative paralysis has numerous associated complications such as upper airway obstruction, aspiration, and hypoxemia.

A recent “Consensus Statement on Perioperative Use of Neuromuscular Monitoring”¹⁴⁹ emphasized that clinical bedside criteria for tracheal extubation (such as a 5-second head lift or ability to generate a peak negative inspiratory force of minus 25–30 cm H₂O) are insensitive indicators of the adequacy of neuromuscular recovery,^{164,165} and that subjective (qualitative) evaluation of the responses to TOF stimulation (when using a PNS) should be abandoned in favor of objective monitoring. Subjective evaluation of the evoked muscular response to TOF and tetanic stimulation are notoriously inaccurate as estimates of fade or postoperative residual neuromuscular blockade.^{166,167} Quantitative monitoring is defined as an objective real-time measurement of the TOFR. The difference between quantitative and qualitative assessments of neuromuscular blockade is in their ability to objectively measure the TOFR. Therefore, the term *monitor* will be restricted to those devices that measure, analyze, and display the TOFR in real time.

Subjective (Qualitative) Evaluation of Neuromuscular Blockade

Visual and/or tactile (subjective) evaluation of evoked responses with the use of a PNS is unreliable at determining recovery from neuromuscular blockade and exposes patients to unnecessary risks associated with residual neuromuscular weakness.¹⁴⁹ Although subjective assessment may help clinicians assess complete block (when posttetanic count = 0), deep block (when posttetanic count ≥ 1 and train-of-four count [TOFC] = 0), and moderate block (TOFC = 1–3), readiness for tracheal extubation (TOFR ≥ 0.90) cannot be assured by subjective evaluation because absence of subjective fade does not consistently identify complete recovery. This modality uses stimulating skin electrodes placed on the skin overlying a superficial motor nerve that innervates the muscle of interest. The negative (typically black) electrode is placed distally to the positive (typically red) electrode (Figures 12.4 and 12.5).¹⁶⁸ Subjective evaluation of TOF stimulation with the use of a PNS requires the observer to determine (1) the number of twitches (TOFC) and (2) the strength of the first response in the train and compare it to the fourth evoked response by tactile or visual means. The TOFC of 1, 2, 3, and 4 corresponds approximately to 10%, 20%, 30%, and 40%, respectively, of single twitch control twitch height.^{169,170} The limitation of TOFR is that once it approaches 0.40, most clinicians cannot detect the presence of fade by subjective assessments and may therefore not administer a reversal drug to ensure adequate recovery of neuromuscular function before tracheal extubation.

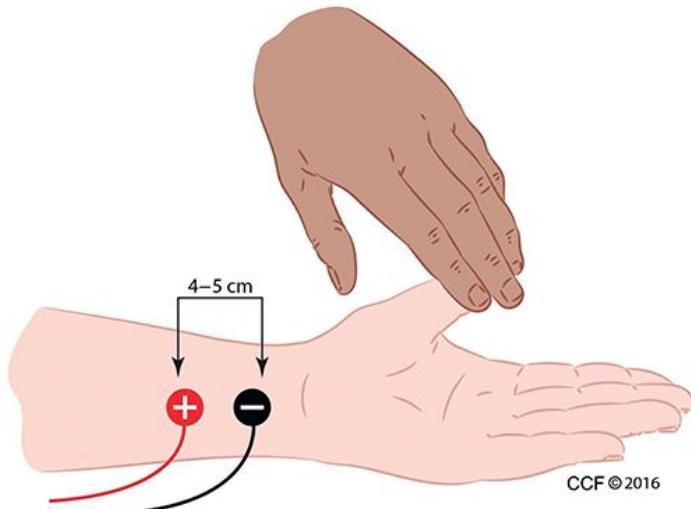


FIGURE 12.4 Subjective (tactile) evaluation of neuromuscular responses at the adductor pollicis (thumb) muscle in response to ulnar nerve stimulation. Note that the black (negative) electrode is distal to the proximal red (positive) electrode. *From Naguib M, Brull SJ, Johnson KB. Conceptual and technical insights into the basis of neuromuscular monitoring. Anaesthesia. 2017;72(Suppl 1):16-37. Reprinted with permission from Cleveland Clinic Center for Medical Art & Photography. Copyright © 2016-2020. All Rights Reserved.*

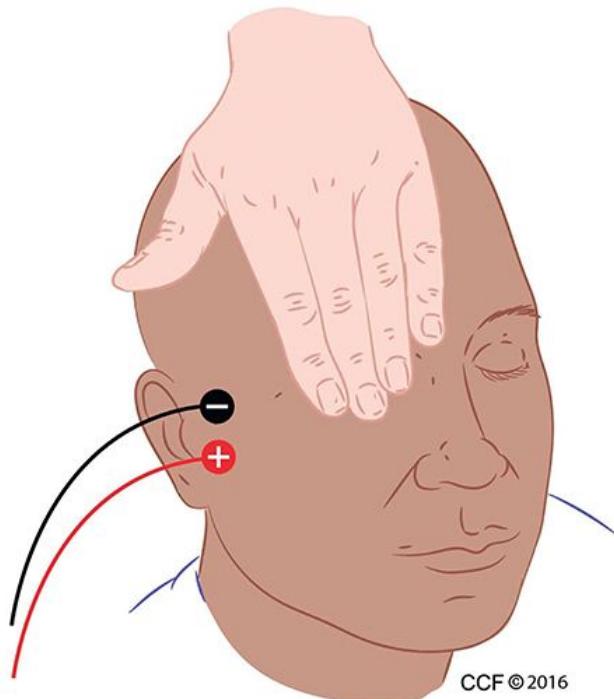


FIGURE 12.5 Subjective (tactile) evaluation of neuromuscular responses at the orbicularis oculi (eye) muscle in response to facial nerve stimulation. Note the negative (black) electrode is placed distally. *From Naguib M, Brull SJ, Johnson KB. Conceptual and technical insights into the basis of neuromuscular monitoring. Anaesthesia. 2017;72(Suppl 1):16-37. Reprinted with permission from Cleveland Clinic Center for Medical Art & Photography. Copyright © 2016-2020. All Rights Reserved.*

Objective (Quantitative) Evaluation of Neuromuscular Blockade

Objective evaluation involves the quantification of the TOFR through the measurement of electrical or mechanical response to nerve stimulation. There are numerous modalities that have been employed to provide such measurements, and the most clinically relevant techniques are discussed here.

Electromyography (EMG) is the oldest form of neuromuscular monitoring; it involves stimulation of a peripheral nerve and measurement of the muscle action potential that is generated by the contraction of the innervated muscle ([Figure 12.6](#)). Active (recording) electrodes are placed over the muscle body, whereas a neutral electrode is placed at a remote site, usually near the muscle insertion site. The EMG signals are subject to electrical interference, direct muscle stimulation, and hypothermia. An EMG is different from other techniques in that there is no muscle movement being analyzed.

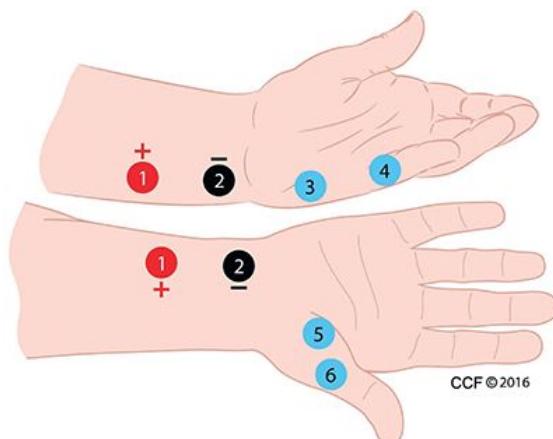


FIGURE 12.6 Placement of the stimulating electrodes (1 and 2) along the ulnar nerve and of the recording electrodes for monitoring the abductor digiti minimi (3 and 4) or the adductor pollicis (5 and 6) muscles by electromyography. *From Naguib M, Brull SJ, Johnson KB. Conceptual and technical insights into the basis of neuromuscular monitoring. Anaesthesia. 2017;72(Suppl 1):16-37. Reprinted with permission from Cleveland Clinic Center for Medical Art & Photography. Copyright © 2016-2020. All Rights Reserved.*

Mechanomyography (MMG) measures the force created by muscle contraction in response to electrical stimuli applied to peripheral nerves ([Figure 12.7](#)). It is regarded as the gold standard of neuromuscular blockade monitoring, and a mechanomyographic adductor pollicis muscle TOFR of 0.9 or more is widely accepted as the threshold for exclusion of residual paralysis. However, its use in clinical settings is limited by stringent preparation and maintenance of a constant preload. An MMG is primarily used for research purposes.

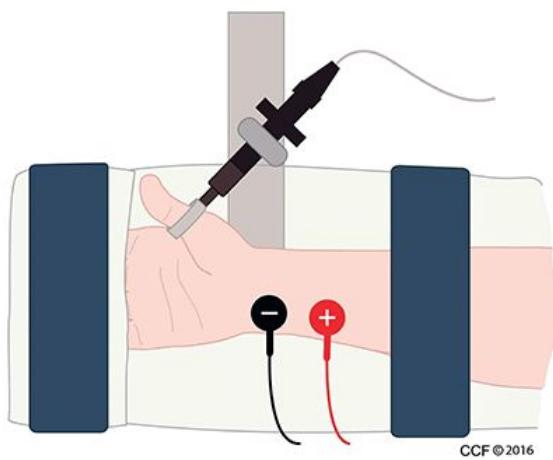


FIGURE 12.7 Apparatus for objective monitoring of the adductor pollicis (thumb) muscle using mechanomyography. A force transducer ring is attached to the thumb, and the fingers are secured to prevent

movement during nerve stimulation. Ulnar nerve stimulation (note that the negative electrode is distal to the positive electrode) will result in contraction of the adductor pollicis muscle, and the force of contraction is measured by the force transducer. The results are displayed on an interfaced screen. *From Naguib M, Brull SJ, Johnson KB. Conceptual and technical insights into the basis of neuromuscular monitoring. Anaesthesia. 2017;72(Suppl 1):16-37. Reprinted with permission from Cleveland Clinic Center for Medical Art & Photography. Copyright © 2016-2020. All Rights Reserved.*

Acceleromyography is based on Newton's second law (force = mass × acceleration) and utilizes a piezoelectric transducer attached to a muscle ([Figure 12.8](#)). An acceleromyography involves measurement of the acceleration of a muscle (usually the adductor pollicis) in response to nerve (usually the ulnar) stimulation. As this technique relies on the free movement of the thumb and requires access to the hand for monitoring, surgical positioning may limit its clinical use.

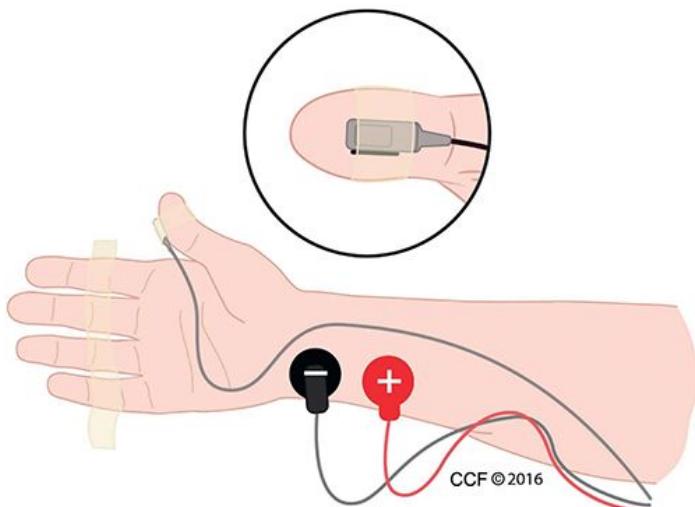


FIGURE 12.8 Apparatus for objective monitoring of the adductor pollicis (thumb) muscle contraction using acceleromyography. An accelerometer is attached to the thumb and the fingers and secured to prevent movement during nerve stimulation. Ulnar nerve stimulation (note that the negative electrode is distal to the positive electrode) will result in contraction of the adductor pollicis muscle, and the thumb acceleration is measured. The results are displayed on the monitor's screen. *From Naguib M, Brull SJ, Johnson KB. Conceptual and technical insights into the basis of neuromuscular monitoring. Anaesthesia. 2017;72(Suppl 1):16-37. Reprinted with permission from Cleveland Clinic Center for Medical Art & Photography. Copyright © 2016-2020. All Rights Reserved.*

Kinemyographic device is based on a mechanosensor strip that contains a piezoelectric polymer ([Figure 12.9](#)). The strip is placed between the base of the thumb and the base of the index finger. When the sensor is bent and exposed to motion, it generates an electrical signal that is proportional to the magnitude of bending; the results are then analyzed. Commercially available devices are versatile and mobile and can be integrated into anesthesia workstations. However, the resulting measurements have been shown not to correlate with the MMG gold standard, limiting its clinical application.



FIGURE 12.9 Apparatus for objective monitoring of the adductor pollicis (thumb) muscle contraction using kinemyography. A mechanosensor (metallic strip) is placed in the groove between the thumb and index finger; ulnar nerve stimulation produces adductor pollicis muscle contraction that bends the strip, generating a current, which is proportional to the strength of muscle contraction. The results are displayed on the monitor's screen. *From Naguib M, Brull SJ, Johnson KB. Conceptual and technical insights into the basis of neuromuscular monitoring. Anaesthesia. 2017;72(Suppl 1):16-37. Reprinted with permission from Cleveland Clinic Center for Medical Art & Photography. Copyright © 2016-2020. All Rights Reserved.*

Clinical Considerations

The blockades produced by depolarizing and nondepolarizing NMBDs are distinct and can be distinguished by their response to peripheral nerve stimulation ([Figure 12.10](#)). During partial blockade, the depolarizing block induced by succinylcholine is characterized by the absence of both fade (to TOF or tetanic stimulation) and posttetanic potentiation in response to nerve stimulation. During partial blockade, the block produced by nondepolarizing NMBDs is characterized by fade after repeated stimulation as well as the ability to cause posttetanic potentiation in which a 5-second tetanic stimulation produces an amplified subsequent response to stimulation. This tetanic stimulus mobilizes prejunctional calcium and allows for the positive feedback on presynaptic acetylcholine receptors, and previously unavailable acetylcholine is released into the synaptic cleft, producing a transiently exaggerated response. It should be noted that succinylcholine can produce fade or posttetanic potentiation when used in large doses (>10 times ED₉₅), after prolonged exposure (>30 min), or in patients with butyrylcholinesterase deficiency.

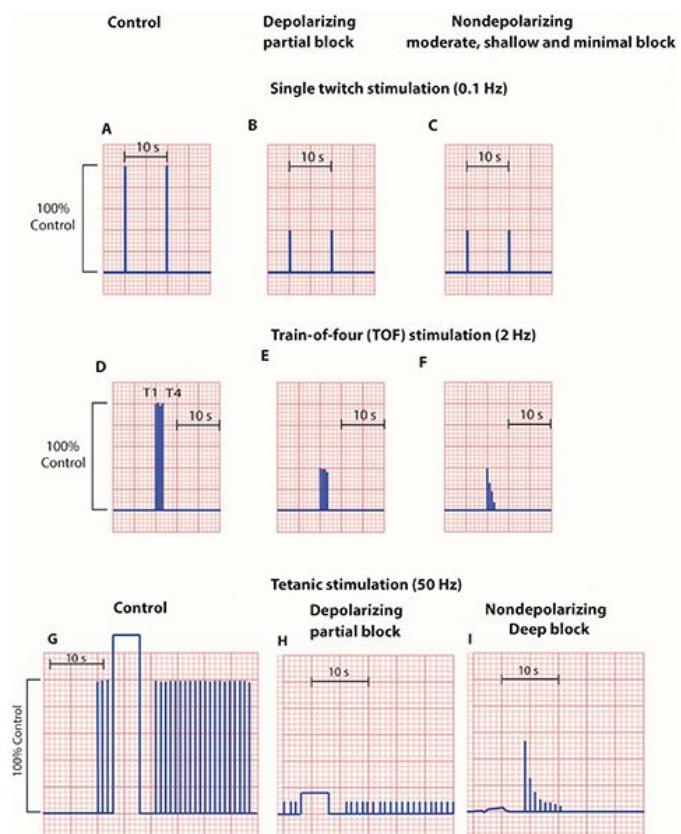


FIGURE 12.10 Depiction of muscle contractions in response to single twitch (ST) stimuli delivered at a frequency of 0.1 Hz during normal conduction (Control, A); partial depolarizing block (B); and moderate, shallow or minimal nondepolarizing block (C). Note the lack of fade between the first ST and subsequent ST evoked responses during both depolarizing and nondepolarizing block when stimuli are delivered at this slow, 0.1-Hz frequency. Train-of-four (TOF) stimulation. The TOF pattern in the absence of neuromuscular block (D, Control). The TOF ratio (TOFR) is calculated as the ratio between the fourth twitch of the TOF sequence (T4) and the first (T1). In the unblocked muscle, the TOF ratio is 1.0. During a partial depolarizing block (E), there is minimal, if any, fade such that the TOF ratio remains close to 1.0. The TOF fade is noted during moderate, shallow, or minimal nondepolarizing block (F). Tetanic stimulation and posttetanic count (PTC). (G) In the unblocked muscle, the mechanical response to a 50-Hz tetanic stimulation is characterized by a sustained contraction with virtually no fade in tetanic response or posttetanic potentiation of twitch response. During partial depolarizing block (H), there is a reduction in the amplitude of tetanic stimulation, but there is no tetanic fade or posttetanic potentiation (I). Application of tetanus during deep block resulted in a faint contraction for 5 seconds, and posttetanic potentiation that results in eight progressively weaker contractions (PTC = 8). Note that when measuring the PTC, one always uses 1-Hz stimulation. From Naguib M, Brull SJ, Johnson KB. *Conceptual and technical insights into the basis of neuromuscular monitoring*. Anaesthesia. 2017;72(Suppl 1):16-37. Copyright © 2017 The Association of Anaesthetists of Great Britain and Ireland. Reprinted by permission of John Wiley & Sons, Inc.

Different muscle groups respond differently to the neuromuscular-blocking effects of NMBDs. Vessel-rich, large, central muscle groups, such as the diaphragm, are more susceptible to NMBD effects than peripheral muscle groups. Thus, these central muscles become paralyzed before peripheral muscles following administration of NMBDs, and they recover faster. Understanding this relationship is essential to monitoring the level of neuromuscular blockade, regardless of which muscles are being monitored. Whether subjective or objective techniques are being used, monitoring the adductor pollicis muscle in response to ulnar nerve

stimulation has been advocated to exclude residual weakness because the adductor pollicis is one of the last muscles to recover from NMBD-induced paralysis.

Compared to peripheral muscles, the laryngeal and diaphragmatic muscles are more resistant to the effects of NMBDs. Neuromuscular blockade develops faster, lasts a shorter time, and recovers faster at the laryngeal and diaphragm muscles compared to the adductor pollicis muscle. The diaphragm and larynx have greater total blood flow than the adductor pollicis muscle, resulting in faster delivery of NMBDs to these muscles. Conversely, washout of NMBDs also occur faster at the central muscles, so recovery occurs here before it does peripherally. Stimulation of the facial nerve will evoke contraction of the orbicularis oculi muscle (the eyelid) as well as the corrugator supercilii muscle (the eyebrow). The corrugator supercilii muscles have the same time course of paralysis and recovery as the laryngeal adductor muscles, whereas the orbicularis oculi muscles time course follows peripheral muscles such as the adductor pollicis.¹⁷¹ Monitoring of facial muscles is a poor substitute for monitoring the adductor pollicis muscle. A recent report showed a 52% incidence of residual paralysis in the recovery room using subjectively assessed eyebrow responses, compared with 22% incidence of residual paralysis during hand muscle monitoring.

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†Deceased.

Neurologically Active Drugs

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Antiepileptic Drugs

Epilepsy is one of the most common neurologic conditions. While 10% of people will report at least one seizure in their lifetime, it is estimated that 1% to 2% of the population worldwide meets the diagnostic criteria for epilepsy ([Table 13.1](#)).¹ Epilepsy is a collective term used to designate a group of chronic central nervous system (CNS) disorders characterized by the onset of sudden disturbances of sensory, motor, autonomic, or psychic origin. These disturbances are usually transient with the exception of status epilepticus and are almost always associated with abnormal discharges on the electroencephalogram. Only 30% of patients with seizures have an identifiable neurologic or systemic disorder.²

TABLE 13.1

Classification of epileptic seizures

Partial seizures (beginning locally)
Simple partial seizures (consciousness not impaired)
Complex partial seizures (consciousness impaired)
Partial seizures evolving into secondary generalized seizures
Generalized seizures (convulsive or nonconvulsive)
Absence seizures (petit mal)
Myoclonic seizures
Clonic seizures
Tonic seizures
Tonic-clonic seizures

Unclassified seizures

Adapted from Brodie MJ, Dichter MA. Antiepileptic drugs. *N Engl J Med.* 1996;334:168-175.

The goal of pharmacologic treatment of epilepsy is to control seizures with minimal medication-related adverse effects. Approximately 70% of patients with epilepsy will become seizure-free using a single antiepileptic drug. For the remaining 30% of patients, further treatment options may include transitioning to another drug; combining the primary drug with an additional drug; or, upon failure of medical therapy, progression to surgical procedures such as a vagal nerve stimulator, laser ablation, implantation of a responsive neurostimulation device, or neurosurgical resection.³ The antiepileptic drug selected to treat epilepsy is highly individualized and tailored to the patient, explaining the high interpatient variability in drug regimens. Criteria that must be considered in choosing an antiepileptic drug include efficacy for the characteristic seizures experienced by the patient, tolerability, safety, ease of use and frequency of administration, and pharmacokinetics ([Table 13.2](#)).³ Over the last several decades, there has been a dramatic increase in drug choices which offer markedly fewer side effects with often comparable efficacy to older drugs improving compliance.^{4,5} However, dose-related side effects can limit the use of any of the antiepileptic drugs ([Table 13.3](#)). Although side effects are normally associated with higher plasma concentrations of the drug, the specific concentration at which a patient develops toxicity varies considerably ([Table 13.4](#)).⁶

TABLE 13.2

Antiepileptic drugs used to treat epilepsy

Drug	Principal mechanism of action	Targeted seizure	Dosage type
Carbamazepine	Sodium ion channel blockade	Partial seizures	10-40 mg/kg per day in 2-3 divided doses

Eslicarbazepine	Sodium ion channel blockade	Partial seizures	800-1,200 mg in 3 divided doses
Ethosuximide	T-type calcium ion change	Generalized seizures	15-40 mg/kg per day in 2-3 divided doses
Felbamate	Sodium ion channel blockade Glutamate antagonism Calcium ion channel blockade	Partial seizures Generalized seizures	15-45 mg/kg per day in 2-3 divided doses
Gabapentin	Unknown	Partial seizures Generalized seizures	10-60 mg/kg per day
Lacosamide	Sodium ion channel blockade	Partial-onset seizures	100-400 mg per day in 3 divided doses
Lamotrigine	Sodium ion channel blockade Calcium ion channel blockade	Partial seizures Generalized seizures	200-500 mg per day in 2 divided doses
Levetiracetam	Unknown (? potassium and calcium ion channel blockade)	Partial seizures Generalized seizures	1,000-3,000 mg per day in 2 divided doses
Oxcarbazepine	Sodium ion channel blockade	Partial seizures Generalized seizures	900-2,400 mg per day in 2 divided doses
Perampanel	AMPA receptor antagonist	Partial seizures Generalized tonic-clonic seizures	24-36 mg per day in 3 divided doses
Phenobarbital	Chloride ion channels	Partial seizures Generalized seizures	2-5 mg/kg per day every day or in 2 divided doses
Phenytoin	Sodium ion channel blockade Calcium ion channels NMDA receptors	Partial seizures Generalized seizures	3-7 mg/kg per day in 3 divided doses
Primidone	Chloride ion channels GABA uptake	Partial seizures Generalized seizures	500-1,500 mg per day in 2-3 divided doses
Rufinamide	Unknown (? sodium channel blockade	Lennox-Gastaut syndrome	400-800 mg per day in 2 divided doses
Stiripentol	Unknown	Dravet syndrome	50 mg/kg per day in 3 divided doses
Tiagabine	Enhanced GABA activity Carbonic anhydrase inhibition	Partial seizures Generalized seizures	32-56 mg/kg per day in 2-4 divided doses
Topiramate	Sodium ion channel blockade Enhanced GABA activity Glutamate antagonism Calcium ion channel blockade	Partial seizures Generalized seizures	500-3,000 mg per day in 2-4 divided doses
Valproate	Sodium ion channel blockade Calcium ion channels	Partial seizures Generalized seizures	500-3,000 mg per day in 2-4 divided doses
Vigabatrin	GABA transaminase inhibition	Complex partial Infantile spasms	3,000 mg per day in 2 divided doses
Zonisamide	Sodium ion channel blockade	Partial seizures	200-600 mg per day in 2-4

	Calcium ion channel blockade	Generalized seizures	divided doses
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Abbreviations: AMPA, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; GABA, γ -aminobutyric acid; NMDA, *N*-methyl-D-aspartate.

TABLE 13.3

Side effects of antiepileptic drugs

	Dose-related	Idiosyncratic
Carbamazepine	Diplopia Vertigo Neutropenia Nausea Drowsiness Hyponatremia	Agranulocytosis Aplastic anemia Allergic dermatitis (rash) Stevens-Johnson syndrome Hepatotoxic effects Pancreatitis Teratogenicity
Eslicarbazepine	Fatigue Dizziness Diarrhea Nausea Vomiting Suicidal thoughts	Allergic dermatitis (rash) Heart block Hyponatremia
Ethosuximide	Nausea Anorexia Vomiting Agitation Headache Drowsiness	Agranulocytosis Aplastic anemia Allergic dermatitis (rash) Stevens-Johnson syndrome Lupus-like syndrome
Clonazepam	Sedation Vertigo Hyperactivity (children)	Allergic dermatitis (rash) Thrombocytopenia
Felbamate	Insomnia Anorexia Nausea Headache Irritability	Aplastic anemia Hepatotoxic effects
Gabapentin	Sedation Ataxia Vertigo Gastrointestinal disturbances	
Lacosamide	Nausea Vomiting Diarrhea Dizziness Irritability Headache Rash	Postural hypotension Cardiac arrhythmias
Lamotrigine	Tremor Vertigo Diplopia Ataxia	Stevens-Johnson syndrome

	Headache Gastrointestinal disturbances	
Levetiracetam	Sedation Anxiety Headache	Allergic dermatitis (rash)
Oxcarbazepine		Allergic dermatitis (rash)
Perampanel	Mood change Dizziness Fatigue Vertigo Slurred speech Euphoria	
Phenobarbital	Sedation Depression Hyperactivity (children)	Agranulocytosis Allergic dermatitis (rash) Stevens-Johnson syndrome Arthritic changes Hepatotoxic effects Teratogenicity
Phenytoin	Nystagmus Ataxia Nausea and vomiting Gingival hyperplasia Depression Megaloblastic anemia Drowsiness	Agranulocytosis Aplastic anemia Allergic dermatitis (rash) Stevens-Johnson syndrome Hepatotoxic effects Pancreatitis Acne Coarse facies Hirsutism Teratogenicity Dupuytren contracture
Primidone	Sedation	Rash Thrombocytopenia Agranulocytosis Lupus-like syndrome Teratogenicity
Rufinamide	Drowsiness Loss of coordination Headache Vomiting	Allergic dermatitis (rash)
Stiripentol	Drowsiness Ataxia Weight loss Fatigue	Elevated γ -glutamyltransferase Neutropenia
Tiagabine	Dizziness Aphasia Tremor	Allergic dermatitis (rash)
Topiramate	Sedation Ataxia Dizziness	Allergic dermatitis (rash)
Valproic acid	Tremor Weight gain Dyspepsia	Agranulocytosis Aplastic anemia Allergic dermatitis (rash)

	Nausea and vomiting Alopecia Peripheral edema Encephalopathy Teratogenicity Sedation	Stevens-Johnson syndrome Hepatotoxic effects Pancreatitis
Vigabatrin	Anemia Sedation Permanent visual loss	
Zonisamide	Teratogenicity Dizziness Ataxia Nephrolithiasis Hyperactivity (children) Mania (adults)	Allergic dermatitis

Adapted in part from Brodie MJ, Dichter MA. Antiepileptic drugs. *N Engl J Med.* 1996;334:168-175, and Dichter MA, Brodie MJ. New antiepileptic drugs. *N Engl J Med.* 1996;334:1583-1590.

TABLE 13.4

Pharmacokinetics of antiepileptic drugs

	Plasma therapeutic concentration ($\mu\text{g}/\text{mL}$)	Protein binding (%)	Elimination half-time (hours)	Route of elimination
Carbamazepine	6-12	70-80	8-24	Hepatic metabolism (active metabolite)
Clonazepam	0.02-0.08	80-90	30-40	Hepatic metabolism
Diazepam		95	20-35	Hepatic metabolism (active metabolites)
Eslicarbazepine		40	10-20	Renal excretion
Ethosuximide	40-100	0	20-60	Hepatic metabolism (25% excreted unchanged)
Felbamate		22-25	20-23	Renal excretion
Gabapentin	2-20	0	6	Renal excretion
Lacosamide		20	10-14	Renal excretion
Lamotrigine		54	25	Hepatic metabolism
Lorazepam		80	14	Hepatic metabolism
Oxcarbazepine		40	8-10	Renal excretion
Perampanel		95	100-110	Hepatic metabolism
Phenobarbital	10-40	48-54	72-144	Hepatic metabolism (25% excreted unchanged)
Phenytoin	10-20	90-93	9-40	Saturable hepatic metabolism
Primidone	5-12	20-30	4-12	Hepatic metabolism to active metabolites of which 40% are excreted unchanged
Rufinamide		30-40	10	Hepatic metabolism
Stiripentol		99	10-15	Hepatic metabolism
Tiagabine		95	5-8	Hepatic metabolism
Topiramate		10	8-15	Renal excretion and hepatic metabolism
Valproic acid	50-100	88-92	7-17	Hepatic metabolism (active metabolites)
Zonisamide		50	50-70	Hepatic metabolism

Adapted in part from Brodie MJ, Dichter MA. Antiepileptic drugs. *N Engl J Med*. 1996;334:168-175 and Dichter MA, Brodie MJ. New antiepileptic drugs. *N Engl J Med*. 1996;334:1583-1590.

Pharmacokinetics

All antiepileptic drugs are administered once daily or more frequently. Sustained release, as well as combination, preparations are becoming increasingly available and preferred by patients because of their ease of use and side effect profile. Absorption of these drugs from the gastrointestinal tract occurs slowly over a period of hours and may be incomplete, especially for gabapentin. Protein binding varies greatly (0% for gabapentin to 90% or greater for phenytoin). Hepatic and renal disease may necessitate dose adjustment. Medications that rely on renal excretion include gabapentin, pregabalin, levetiracetam, vigabatrin, and zonisamide and should be dosed according to renal function. The remainder of medications is hepatically metabolized and should be dosed according to the patient's degree of liver dysfunction.

Antiepileptic drug clearance and elimination half-time range from hours (carbamazepine, valproate, primidone, gabapentin) to days (phenytoin, lamotrigine, phenobarbital, zonisamide) (see [Table 13.4](#)). Because of their ability to induce or inhibit drug metabolism, all antiepileptic drugs, except gabapentin, levetiracetam, and vigabatrin, may be associated with pharmacokinetic drug interactions in which plasma drug concentrations and resulting pharmacologic effects of concomitantly administered drugs may be altered. Such drug interactions should be anticipated in all patients receiving antiepileptic drugs and subsequently receiving drugs for other purposes.

Drug Interactions Related to Protein Binding

Medications that compete for protein binding sites of highly bound antiepileptic drugs (phenytoin, valproate, carbamazepine) can displace the bound drug and lead to increases in the plasma concentration of pharmacologically active antiepileptic drug. Commonly used medications that are highly protein bound include thyroxine and salicylates. Albumin is the principal binding protein for antiepileptic drugs. Hypoalbuminemia, as may accompany renal or hepatic disease or malnutrition, can result in increased plasma concentrations of unbound antiepileptic drug, resulting in toxicity despite therapeutic plasma concentrations. In pregnancy, hypoalbuminemia due to a progressive increase in central volume offsets the dilutional effect.

Drug Interactions Related to Accelerated Metabolism

Enzyme-inducing antiepileptic drugs that accelerate metabolism (carbamazepine, lamotrigine oxcarbazepine, phenobarbital, phenytoin, topiramate, primidone) may accelerate the metabolism of estrogen and progesterone and thus render oral contraceptives ineffective at usual doses. Patients being treated with antiepileptic drugs have increased dose requirements for thiopental, propofol, midazolam, opioids, and nondepolarizing neuromuscular-blocking drug. Possible explanations for altered dose requirements for drugs administered during anesthesia include increased hepatic P450 enzyme activity as a result of stimulating effects of antiepileptic drugs, alterations in the number and/or responsiveness of receptors, and interactions with endogenous neurotransmitters.

Principles of Dosing

The initial dose is that which is high enough to expect clinical effect but low enough to avoid significant side effects (see [Table 13.3](#)). Gradual dose titration is recommended in all but emergency situations. The clinical response guides dose adjustment over time, as there is significant variability in clinical response over a wide range of dosages. A common cause of medication ineffectiveness is failure to achieve a sufficiently high plasma concentration. Noncompliance is a particular concern in specific patient populations including adolescents and the elderly.^{13.6}

To maintain plasma drug concentrations in a therapeutic range, equal doses of the antiepileptic drug are often administered at intervals equivalent to less than one elimination half-time of the drug (see [Table 13.4](#)). Dosing at one-half the drug's elimination half-time ensures that a single missed dose will not result in the plasma concentration decreasing below a therapeutic level.

Plasma Concentrations and Laboratory Testing

Phenytoin is the only agent for which monitoring is routinely recommended due to its nonlinear saturation dose kinetics. Routine laboratory monitoring of plasma concentrations for all other agents is not recommended.³ For this reason, titration to clinical efficacy is recommended for guiding the dosages of antiepileptic drugs. Some patients may respond at low plasma concentrations, and some patients will not respond until high plasma concentrations are obtained. If a patient does not respond to a particular drug as expected, investigating the plasma drug concentration may aid in determining compliance and identifying potential pharmacokinetic interactions.^{1,6}

Mechanism of Seizure Activity

Seizure activity in most patients with epilepsy has a localized or focal origin. Magnetic resonance imaging is the imaging modality of choice, and up to half of newly diagnosed patients with epilepsy exhibit an epileptogenic focus. The reason for the high frequency and synchronous firing in a seizure focus is usually unknown. Possible explanations include local biochemical changes, ischemia, loss of cellular inhibitory systems, infections, and head trauma.

Neurons in a chronic seizure focus exhibit a type of denervation hypersensitivity with regard to excitatory stimuli. The spread of seizure activity to neighboring normal cells is presumably restrained by normal inhibitory mechanisms. Factors such as changes in blood glucose concentrations, PaO_2 , Paco_2 , pH, electrolyte balance, endocrine function, stress, and fatigue may facilitate the spread of a seizure focus into areas of the normal brain. If the spread is sufficiently extensive, the entire brain is activated and a tonic-clonic seizure with unconsciousness ensues. Conversely, if the spread is localized, the seizure produces signs and symptoms characteristic of the anatomic focus. Once initiated, a seizure is most likely maintained by reentry of excitatory impulses in a closed feedback pathway that may not even include the original seizure focus.

Mechanism of Drug Action

The mechanism of action of antiepileptic drug activity is incompletely understood. It is commonly presumed that antiepileptic drugs control seizures by decreasing neuronal excitability or enhancing inhibition of neurotransmission. This is achieved by altering intrinsic membrane ion currents (sodium, potassium, and calcium conductance) or by affecting activity of inhibitory neurotransmitters. Ion currents affected by antiepileptic drugs are primarily those involving the voltage-gated sodium and calcium ion channels. Drugs that delay reactivation of sodium channels (phenytoin, carbamazepine, primidone, valproate, lamotrigine) during high-frequency neuronal firing produce an inhibitory effect on creation of action potentials until neuronal discharge is blocked. Some drugs (phenytoin, carbamazepine, valproate, lamotrigine, zonisamide) act at both sodium and calcium ion channels. Other drugs (ethosuximide, phenobarbital) act selectively at calcium ion channels. Ethosuximide selectively blocks the T-type calcium ion current, which is thought to act as a pacemaker for thalamic neurons and may be important in absence seizures. Drugs (phenobarbital, benzodiazepines) that alter synaptic function act primarily by enhancing γ -aminobutyric acid (GABA)-mediated neuronal inhibition. Benzodiazepines increase the frequency of GABA-mediated ion channel openings, whereas barbiturates increase the duration of ion channel openings. Tiagabine delays the reuptake of GABA from synaptic clefts, effectively enhancing GABA-mediated neuronal inhibition after synaptic release of the neurotransmitter.

Major Antiepileptic Drugs

The principal antiepileptic drugs used to treat patients with epilepsy are carbamazepine, clobazam, eslicarbazepine, ethosuximide, felbamate, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, phenobarbital, phenytoin, pregabalin, primidone, rufinamide, stiripentol, tiagabine, topiramate, valproate, vigabatrin, and zonisamide (see [Table 13.2](#)). Since 2005, the number of agents has more than doubled, thereby offering broader therapeutic with fewer drug interactions, broader spectrums of activity, and unique mechanisms of action (see [Table 13.3](#)).^{2,7}

Benzodiazepines such as diazepam, lorazepam, and midazolam are used for short-term treatment of acute seizures or status epilepticus and are usually administered parenterally. Clonazepam can be used to treat

epilepsy, but most patients develop tolerance to its antiepileptic effects and sedation is a common side effect. Felbamate is reserved for use in selected patients with uncontrolled seizures due to its side effect profile. Clobazam is a more recent addition to this class and is unique among other members of the class in that it does not induce significant levels of sedation and can be used for long-term therapy because tolerance is relatively uncommon.⁸

Drugs used in the treatment of partial seizures are carbamazepine, lamotrigine, oxcarbazepine, topiramate, zonisamide, and phenytoin, which are highly effective and associated with an acceptable side effect profile (see [Table 13.2](#)). Valproate, lamotrigine, and topiramate are the antiepileptic drugs useful for treatment of patients with generalized seizures. Ethosuximide, lamotrigine, or valproate are effective in treatment of patients with generalized nonconvulsive seizures, especially absence seizures.

Adverse Side Effects

Antiepileptic drugs may potentially produce numerous and varied adverse side effects related to their mechanism of action and off target effects. Newer agents have a significantly more favorable side effect profile. Some adverse side effects are dose related (sedation, lethargy, neurotoxicity), whereas others are idiosyncratic (hypersensitivity, hepatotoxicity, aplastic anemia) (see [Table 13.3](#)).

Maternal Epilepsy

Unintended pregnancy can result from enzyme inducing antiepileptic drugs that render oral contraceptive pills less effective. Seizures during pregnancy can result in significant morbidity and mortality to both mother and fetus, making seizure control during this period imperative.³ Monotherapy with the lowest dose possible is the guiding principle. Fetal organogenesis is largely complete by 8 weeks. Significant teratogenicity may occur during this period if pregnancy is not detected early enough to permit discontinuation of potentially teratogenic medications. Drug regimens in women of childbearing age should therefore be given special attention. In particular, parturients who take valproate have more than double the risk of giving birth to a fetus with congenital malformations including neural tube defects such as spina bifida, atrial septal defects, cleft palate, hypospadias, polydactyly, and craniosynostosis. Other antiepileptics that should be avoided during pregnancy because of risk of malformation rates include phenytoin and phenobarbital. Patients on less than 300 mg per day of lamotrigine or less than 400 mg per day of carbamazepine have rates of congenital malformation comparable to the general population. Clobazam may be added as needed especially during labor. Conclusive data regarding other antiepileptic drugs during pregnancy is lacking, in part due to the ethical and regulatory difficulty of conducting randomized trials during pregnancy.¹ Folate supplementation during pregnancy lowers the risk of teratogenicity in babies born to women who are taking antiepileptic medications.⁹

Carbamazepine

Carbamazepine is an iminostilbene derivative that is effective for suppression of nonconvulsive and convulsive partial and generalized seizures. In addition, this drug may be useful in the management of patients with trigeminal neuralgia and glossopharyngeal neuralgia. Structurally, carbamazepine is related to the tricyclic antidepressant imipramine. Like phenytoin, carbamazepine maintains sodium channels in their inactive conformation, which prevents repetitive and sustained firing of an action potential.

Pharmacokinetics

This drug is available only as an oral preparation (see [Table 13.4](#)). Oral absorption is rapid, with peak plasma concentrations occurring 2 to 6 hours after ingestion. Plasma protein binding is 70% to 80%. The plasma elimination half-time is 8 to 24 hours. The principal metabolite of carbamazepine is an epoxide derivative that has antiseizure effects that may also be responsible for many of the dose-limiting side effects of this drug. Because this drug induces its own metabolism, many patients require a dosage increase in 2 to 4 weeks after initiation of therapy. The usual therapeutic plasma concentration of carbamazepine is 6 to 12 µg/mL.

Side Effects

The toxicity of carbamazepine is similar to that produced by phenytoin (see [Table 13.3](#)). Sedation, vertigo, diplopia, nausea, and vomiting are the most frequent side effects of this drug. Chronic diarrhea develops in some patients, whereas others experience the syndrome of inappropriate antidiuretic hormone secretion. Aplastic anemia, thrombocytopenia, hepatocellular and cholestatic jaundice, oliguria, hypertension, and cardiac dysrhythmias are rare but potentially life-threatening complications. Chronic suppression of white blood cell counts can occur. For these reasons, it may be prudent to monitor bone marrow, cardiac, hepatic, and renal function in patients being treated with carbamazepine. At high plasma concentrations, carbamazepine has an arginine vasopressin hormone-like action that may result in hyponatremia. Skin rash, often with other manifestations of drug allergy, occurs in approximately 10% of chronically treated patients.

In addition to inducing its own metabolism, carbamazepine can accelerate the hepatic oxidation and conjugation of other lipid-soluble drugs. The most common interaction is with oral contraceptive pills, and most women require an increase in the daily dose of estrogen. Carbamazepine also accelerates the metabolism of valproic acid, ethosuximide, corticosteroids, anticoagulants, and antipsychotic drugs. Drugs that inhibit the metabolism of carbamazepine sufficiently to cause toxic effects include cimetidine, propoxyphene, diltiazem, verapamil, isoniazid, and erythromycin.

Eslcarbazepine

Eslcarbazepine is approved for use for partial-onset seizures. Its mechanisms of action also involve stabilization of the inactive state of voltage-gated sodium channels. This allows less sodium to enter the neuron, which reduces excitability. Upon oral administration, it is absorbed greater than 90% and is metabolized to eslicarbazepine, and peak plasma concentration occurs in 2 to 4 hours. It is 40% plasma protein bound. Excretion is 90% by the kidneys. The most common side effects are dizziness and fatigue, diarrhea, nausea, vomiting, rash, and hyponatremia. Eslcarbazepine is contraindicated in patients with second- or third-degree atrioventricular heart block as it may cause lethal cardiac arrhythmias. Carbamazepine and phenytoin reduce the plasma concentration of eslicarbazepine because of the induction of hepatic glucuronidation.[10,11](#)

Ethosuximide

Ethosuximide is the drug of choice for suppression of absence (petit mal) epilepsy in patients who do not also have tonic-clonic seizures. This drug acts by decreasing voltage-dependent calcium conductance in thalamic neurons. This is consistent with the speculated importance of the thalamocortical system in the etiology of absence seizures.

Pharmacokinetics

This drug is available only as an oral preparation (see [Table 13.4](#)). Peak plasma concentrations occur in 1 to 7 hours after oral administration. Ethosuximide is not significantly bound to albumin. Approximately 25% of the drug is excreted unchanged in urine, and the remainder is metabolized to inactive metabolites by hepatic microsomal enzymes. The elimination half-time is 20 to 60 hours. The usual maintenance dose of ethosuximide is 20 to 30 mg/kg. A plasma concentration of 40 to 100 µg/mL is required for satisfactory suppression of absence epilepsy.

Side Effects

Toxicity of ethosuximide is low, manifesting most often as gastrointestinal intolerance (nausea, vomiting) and CNS effects (lethargy, dizziness, ataxia, photophobia). There have been rare reports of bone marrow suppression. Hyponatremia is also a possible side effect.[9](#)

Felbamate

Because of its potential to produce life-threatening side effects, felbamate is not used as a first-line drug for treatment of seizures but rather is reserved for patients with intractable epilepsy. Felbamate is used principally for poorly controlled partial and secondarily generalized seizures. It also decreases the frequency of seizures associated with the Lennox-Gastaut syndrome and myotonic and atonic forms of epilepsy.[12](#) The mechanism

of action of felbamate is unknown but may involve action at voltage-gated sodium channels, *N*-methyl-D-aspartate and non-*N*-methyl-D-aspartate glutamate receptors, voltage-gated calcium currents, and GABA receptor modulation.⁸

Pharmacokinetics

Oral absorption is prompt and the elimination half-time is prolonged (see [Table 13.4](#)). Felbamate undergoes minimal metabolism with most of the drug being excreted unchanged by the kidneys.

Side Effects

Serious side effects include aplastic anemia and hepatotoxicity (see [Table 13.3](#)). Monitoring of treated patients with complete blood counts and liver function tests is indicated. Because felbamate is metabolized by hepatic cytochrome P450 enzymes, its metabolism is affected by concurrent administration of other drugs that are also metabolized by this system. In particular, concomitant administration of carbamazepine or phenytoin may decrease plasma concentrations of felbamate. Likewise, because felbamate is a potent inhibitor of P450 enzymes, it can slow the metabolism of phenytoin, phenobarbital, and valproic acid. In this regard, if a patient is receiving phenytoin, carbamazepine, or valproic acid and receives felbamate, the dose of these drugs should be decreased by 20% to 30% to prevent toxic effects.

Gabapentin

The pharmacokinetic considerations for gabapentin are discussed in detail in Chapter 2. Gabapentin is an analogue of GABA but does not bind to GABA receptors. Its mechanism of action is largely unknown but likely involves inhibition of voltage-gated calcium channels. Gabapentin induces dose-related sedation, and it has efficacy in the treatment of anxiety, panic, and major depression.¹³ Despite its multiple other uses, gabapentin has limited efficacy in the treatment of epilepsy.

Lacosamide

Lacosamide is indicated for partial-onset seizures. Its mechanism of action is through voltage-gated sodium channels. Specifically, it enhances the slow inactivation of voltage-gated sodium channels, thereby preventing the action potential from occurring. Because it prevents the sodium channel from opening on neurons, which are firing action potentials, it is able to effectively stabilize hyperexcitable neurons. Lacosamide is rapidly absorbed from the gastrointestinal tract and reaches peak plasma concentrations 2 to 5 hours after administration. It has a bioavailability of almost 100%. It has few drug interactions due to low plasma protein binding of less than 20%. It is excreted 95% in the urine. The most common side effects are nausea, vomiting, diarrhea, dizziness, headaches, drowsiness, postural hypotension, arrhythmias, itching, and rash.^{14,15}

Lamotrigine

Lamotrigine is a chemically novel anticonvulsant drug of the phenyltriazine class that most likely acts by stabilizing voltage-sensitive sodium ion channels, thus preventing release of aspartate and glutamate. This drug has a broad spectrum of activity and is effective when used alone or in combination in adults who have partial seizures or generalized seizures and in children with Lennox-Gastaut syndrome. When administered orally, lamotrigine is well absorbed, and its plasma elimination half-time is about 25 hours (see [Table 13.4](#)). Drugs that induce hepatic microsomal enzymes (phenobarbital, phenytoin, and carbamazepine) decrease the elimination half-time of lamotrigine by about 50%, necessitating a higher dose. Conversely, valproic acid slows the metabolism of lamotrigine and extends its elimination half-time to about 60 hours. The most common side effects of lamotrigine are headache, nausea, vomiting, dizziness, diplopia, and ataxia (see [Table 13.3](#)). Tremor can be troublesome at higher doses. In approximately 5% of adults, a rash develops, which subsequently disappears in some patients, despite continued therapy. In a few patients, however, the rash is more serious, and fever, arthralgias, and eosinophilia occur. In rare cases, Stevens-Johnson syndrome has been reported.

Levetiracetam

Levetiracetam is available in both oral and intravenous (IV) preparations. It is effective in the management of juvenile myoclonic epilepsy, partial and generalized convulsive seizures, generalized tonic-clonic seizures, and partial seizures. Its mechanism of action is not fully known; however, it binds to certain presynaptic calcium channels, acting to reduce synaptic neurotransmitter release.¹⁶ Side effects are considered minor and include sedation, asthenia, anxiety, and headache. The pharmacokinetic profile of levetiracetam is favorable, with the absence of hepatic metabolism and minimal protein binding. No significant drug interactions have been described with coadministration of other antiepileptic drugs.

Oxcarbazepine

Oxcarbazepine is a keto analogue of carbamazepine that provides equivalent seizure control but with fewer adverse side effects. After administration, oxcarbazepine acts as a prodrug that is converted to an active metabolite, 10-hydroxycarbazepine. Oxcarbazepine and its active metabolite do not induce hepatic microsomal enzymes nor does it displace other drugs from plasma protein binding sites. As such, they are safer drugs to be used in combination therapy.

Perampanel

Perampanel is indicated for patients with partial seizures and generalized tonic-clonic seizures. It has a unique mechanism of action that involves the selective noncompetitive antagonism of α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors. Perampanel is 95% plasma protein bound and has an elimination half-life of 110 hours. It is primarily metabolized by the liver and is excreted in the feces (70%) and urine (30%). A black box warning exists that some patients may experience suicidal or homicidal thoughts. Other side effects include dizziness, fatigue, vertigo, slurred speech, irritability, and aggression. In high doses, it can produce a euphoric sensation; therefore, it can be potentially abused.^{17,18}

Phenobarbital

Phenobarbital is a long-acting barbiturate that is effective against all seizure types except nonconvulsive primary generalized seizures. Cognitive and behavioral side effects limit this drug's usefulness in the treatment of epilepsy. Because of these side effects, phenobarbital is considered a second-line drug in the treatment of epilepsy.

Phenobarbital appears to exert its antiepileptic properties partly through potentiation of the postsynaptic actions of the inhibitory neurotransmitter GABA and inhibition of the excitatory postsynaptic actions of glutamate. These drug-induced effects prolong the duration of chloride channel opening and thus limit the spread of seizure activity and increase the seizure threshold.

Pharmacokinetics

Oral absorption of phenobarbital is slow but nearly complete, with peak concentrations occurring 12 to 18 hours after a single dose (see [Table 13.4](#)). Plasma protein binding is 48% to 54%. Approximately 25% of phenobarbital is eliminated by pH-dependent renal excretion, with the remainder inactivated by hepatic microsomal enzymes. The principal metabolite is an inactive parahydroxyphenyl derivative that is excreted in urine as a sulfate conjugate. The elimination half-time of phenobarbital is prolonged.

The usual daily oral dose of phenobarbital is 60 mg in adults or 4 mg/kg in children. Plasma phenobarbital concentrations of 10 to 40 μ g/mL are usually necessary for control of seizures. The value of measuring plasma phenobarbital concentrations is limited because the concentration associated with optimal control is highly variable among patients. In addition, the development of tolerance to the drug's CNS effects makes the toxic threshold imprecise.

Side Effects

Sedation in adults and children and irritability and hyperactivity in children are the most troublesome side effects when this drug is used to treat epilepsy (see [Table 13.3](#)). Tolerance to the sedative effects of phenobarbital may develop with chronic therapy. Depression develops in many adults taking phenobarbital,

and confusion may occur in elderly patients. Cognitive effects include slowing of task processing. Scarlatiniform or morbilliform rash occurs in up to 2% of patients. Megaloblastic anemia that responds to folic acid administration and osteomalacia that responds to vitamin D therapy may occur during chronic phenobarbital therapy as well as during treatment with phenytoin. Nystagmus and ataxia are likely if the plasma phenobarbital concentration is >40 $\mu\text{g}/\text{mL}$. Abnormal collagen deposition manifesting as Dupuytren contracture may occur. Congenital malformations may occur when phenobarbital is administered chronically during pregnancy. Coagulation defects and hemorrhage in the neonate must be considered in the setting of fetal exposure. Interactions between phenobarbital and other drugs usually involve induction of hepatic microsomal enzymes. In this regard, phenobarbital is the classic example of a hepatic microsomal enzyme inducer that can accelerate the metabolism of many lipid-soluble drugs.

Phenytoin

Phenytoin is the prototype of the hydantoins and is effective for the treatment of partial and generalized seizures. Available in oral and IV preparations, phenytoin may be administered acutely to achieve effective plasma concentrations within 20 minutes. This drug has a high therapeutic index, and its administration is not accompanied by excessive sedation.

Mechanism of Action

Phenytoin regulates neuronal excitability and thus the spread of seizure activity from a seizure focus by regulating sodium and possibly calcium ion transport across neuronal membranes. This stabilizing effect on cell membranes is relatively selective for the cerebral cortex, although the effect also extends to peripheral nerves. In addition to the effect on ion fluxes, phenytoin acts on second messengers such as calmodulin and the cyclic nucleotides.

Pharmacokinetics

Phenytoin is a weak acid ($\text{pK } 8.3$) that is maintained in aqueous solutions as a sodium salt (see [Table 13.4](#)). The drug precipitates in solutions with a pH of <7.8 . Its poor water solubility may result in slow and sometimes variable absorption from the gastrointestinal tract (30%-97%). The initial daily adult oral dosage is 3 to 4 mg/kg . Doses of >500 mg daily are rarely tolerated. The long duration of action of phenytoin allows a single daily dosage, but gastric intolerance may necessitate divided dosage. After intramuscular (IM) injection, the drug precipitates at the injection site and is slowly absorbed. For this reason, IM administration is not recommended. Infusion of phenytoin should probably not exceed 5 mg per minute.

Plasma Concentrations

Control of seizures is usually obtained when plasma concentrations of phenytoin are 10 to 20 $\mu\text{g}/\text{mL}$. In the control of digitalis-induced cardiac dysrhythmias, phenytoin, 0.5 to 1.0 mg/kg IV, is administered every 15 to 30 minutes until a satisfactory response is achieved or a maximum dose of 15 mg/kg is administered. A plasma phenytoin concentration of 8 to 16 $\mu\text{g}/\text{mL}$ is usually sufficient to suppress cardiac dysrhythmias. Adverse side effects of phenytoin such as nystagmus and ataxia are likely when the plasma concentration of drug >20 $\mu\text{g}/\text{mL}$. Nevertheless, the diagnosis of phenytoin toxicity should be made on the basis of clinical symptoms.

Protein Binding

Phenytoin is bound approximately 90% to plasma albumin. A greater fraction of phenytoin remains unbound in neonates, in patients with hypoalbuminemia, and in uremic patients.

Metabolism

Metabolism of phenytoin to inactive metabolites is by hepatic microsomal enzymes that are susceptible to stimulation or inhibition by other drugs. An estimated 98% of phenytoin is metabolized to the inactive derivative parahydroxyphenyl, which appears in urine as a glucuronide. Approximately 2% of phenytoin is recovered unchanged in urine.

When the plasma concentration of phenytoin is <10 µg/mL, metabolism follows first-order kinetics, and the elimination half-time averages 24 hours. At plasma concentrations of >10 µg/mL, the enzymes necessary for metabolism of phenytoin become saturated, and the elimination half-time becomes dose-dependent (zero-order kinetics). At this stage, relatively small increases in dose may result in dramatic increases in the plasma concentration of phenytoin. Zero-order kinetics in phenytoin metabolism resembles the metabolism of alcohol.

Side Effects

The side effects of phenytoin include CNS toxicity that manifests clinically as nystagmus, ataxia, diplopia, and vertigo (cerebellar-vestibular dysfunction) and is likely when the plasma phenytoin concentration is >20 µg/mL. Peripheral neuropathy has been observed in up to 30% of chronically treated patients. Gingival hyperplasia occurs in approximately 20% of chronically treated patients and is probably the most common manifestation of phenytoin toxicity in children and adolescents. This complication is minimized by improved oral hygiene and does not necessarily require discontinuation of phenytoin therapy. Other reversible cosmetic side effects include acne, hirsutism, and facial coarsening. Administration of phenytoin during pregnancy may result in the fetal hydantoin syndrome, which manifests as wide-set eyes, broad mandible, and finger deformities.

Allergic reactions include morbilliform rash in 2% to 5% of patients. Hyperglycemia and glycosuria may reflect phenytoin-induced inhibition of insulin secretion. Megaloblastic anemia is rare and has been attributed to altered folic acid absorption but probably also involves altered folic acid metabolism. Phenytoin-induced hepatotoxicity, although rare, may occur in genetically susceptible persons who lack the enzyme phenytoin epoxide. This enzyme is necessary to convert an electrophilic intermediate formed after the oxidative metabolism of phenytoin to an inert and nontoxic product. Gastrointestinal irritation is due to alkalinity of the drug; this may be minimized by taking phenytoin after meals.

Phenytoin can induce the oxidative metabolism of many lipid-soluble drugs, including carbamazepine, valproic acid, ethosuximide, anticoagulants, and corticosteroids. Because its metabolism is saturable, inhibitory interactions are particularly likely to have neurotoxic effects. Interactions involving protein binding displacement are not likely to be clinically significant.

Patients receiving phenytoin chronically have higher dose requirements for nondepolarizing neuromuscular-blocking drugs such as vecuronium compared with untreated patients. Phenytoin induces hepatic enzymes and it is likely that metabolism and elimination of nondepolarizing neuromuscular-blocking drugs is increased. Phenytoin may also produce mild blocking effects at the neuromuscular junction leading to upregulation of acetylcholine receptors.

Primidone

Primidone is metabolized to phenobarbital and another active metabolite, phenylethylmalonamide. The efficacy of this drug resembles that of phenobarbital, but it is less well tolerated. There is little to recommend this drug over phenobarbital for patients in whom treatment with a barbiturate is contemplated. Possible side effects include Dupuytren contracture, shortening of the QT segment, and coagulation defects. For this reason, it is seldom prescribed.

Rufinamide

Rufinamide is used as combination therapy in the treatment of Lennox-Gastaut syndrome in children and adults. It has an unknown mechanism of action, owing to its unique chemical structure that is different from all other antiepileptics. It is 30% to 40% protein bound and has an elimination half-life of 10 hours. It is metabolized by the liver via carboxylesterase-mediated hydrolysis and is 90% excreted in the urine. Common side effects include headaches, fatigue, dizziness, and nausea.[19,20](#)

Stiripentol

Stiripentol is approved for the treatment of Dravet syndrome and is typically used as an add-on therapy with valproate or clobazam. It has a unique chemical structure, belonging to the group of aromatic allylic alcohols.

It rapidly crosses the blood–brain barrier and enters the brain, where it accumulates in the cerebellum and medulla. Its mechanism of action is unknown but is known to increase GABAergic activity. Common adverse effects include weight loss, loss of appetite, somnolence, ataxia, hypotonia, and dystonia. Less frequently, neutropenia may occur, and therefore, routine monitoring of a white blood cell counts while on therapy is necessary. Other less common side effects include nausea, vomiting, aggression, hyperexcitability, and sleep disorders.^{[21](#)[22](#)}

Tiagabine

Tiagabine is a nipecotic acid moiety that is a potent inhibitor of GABA reuptake. This drug is used as adjunctive therapy for complex partial seizures. Possible side effects include dizziness, asthenia, aphasia, and tremor. Mental depression may accompany administration of tiagabine perhaps reflecting this drug's ability to increase GABA concentrations. Drug interactions are unlikely despite the high protein binding of tiagabine reflecting the small amount of drug needed to achieve clinical efficacy. Tiagabine has no effect on hepatic enzymes.

Topiramate

Topiramate is a broad-spectrum antiepileptic drug that is indicated as monotherapy or adjunctive therapy in children and adults for the control of partial, generalized tonic-clonic, and absence seizures. Efficacy in treatment of other neurologic and psychiatric disorders has been reported including bulimia, migraine headache, and essential tremor. Topiramate inhibits voltage-gated sodium ion channels, high-voltage activated calcium ion channels, and glutamate-mediated neurotransmission at specific receptor subtypes. In addition, topiramate is a weak inhibitor of carbonic anhydrase. Minor side effects may include sedation, dizziness, and ataxia. Nephrolithiasis occurs in about 1.5% of treated patients perhaps reflecting this drug's action on carbonic anhydrase. Enzyme-inducing drugs decrease plasma concentrations of topiramate, but topiramate does not affect hepatic P450 enzymes and undergoes minimal protein binding.

Valproic Acid

Valproic acid is a branched-chain carboxylic acid that is effective in the treatment of all primary generalized epilepsies and all convulsive epilepsies. It is somewhat less effective for the suppression of nonconvulsive partial seizures. This drug acts by limiting sustained repetitive neuronal firing through voltage-dependent sodium channels.

Pharmacokinetics

Valproic acid is available as a syrup and in an enteric-coated formulation, which is preferred because it decreases gastrointestinal side effects. After oral administration, absorption is prompt, with peak plasma concentrations of valproic acid occurring in 1 to 4 hours. Binding to plasma proteins is >80%. More than 70% of the drug can be recovered as inactive glucuronide conjugates. The elimination half-time is 7 to 17 hours. The usual daily dose of valproic acid is 1 to 3 g to achieve a therapeutic plasma concentration of 50 to 100 µg/mL. Nevertheless, the daily variation in plasma concentrations of valproic acid is great, and routine monitoring may not be helpful unless it is correlated with the patient's clinical condition.

Side Effects

Gastrointestinal side effects include anorexia, nausea, and vomiting. Weight gain is common in patients treated chronically with valproic acid. At higher doses, a fine distal tremor may develop. Thrombocytopenia is seen frequently at higher doses. The most serious side effect of valproic acid is hepatotoxicity occurring in about 0.2% of children younger than 2 years of age being treated chronically with this drug. The incidence of this potentially fatal hepatic necrosis decreases dramatically after 2 years of age. Approximately 20% of treated patients have hyperammonemia without hepatic damage. Sedation and ataxia are infrequent side effects of valproic acid.

Because valproic acid is partly eliminated as a ketone-containing metabolite, the urine ketone test may show false-positive results. Valproic acid can displace phenytoin and diazepam from protein binding sites,

resulting in increased pharmacologic effects produced by the displaced drug.

Valproic acid is an enzyme inhibitor. As a result of this enzyme inhibition, the metabolism of phenytoin is slowed by valproic acid. Valproic acid causes the plasma concentration of phenobarbital to increase almost 50%, presumably due to inhibition of hepatic microsomal enzymes. However, valproic acid does not interfere with the action of oral contraceptives.

Vigabatrin

Vigabatrin is used to treat refractory complex partial seizures. It may also be used as monotherapy to treat infantile spasms. Tablet and powder preparations are available and are bioequivalent. Its mechanism of action is imperfectly understood but is thought to involve irreversible inhibition of the GABA transaminase enzyme, thereby increasing the amount of GABA in the CNS. It is not protein bound and undergoes no significant metabolism. It is excreted unchanged in the urine. Dosage must therefore be adjusted if renal impairment is present. Significant side effects include permanent visual loss, anemia, somnolence, and fatigue.²³

Zonisamide

Zonisamide is a broad-spectrum antiepileptic drug used as adjunctive therapy for management of partial and secondarily generalized seizures. Modulation of voltage-dependent calcium ion channels seems to be an important mechanism for this drug's ability to control seizures. In addition, zonisamide enhances GABA-mediated neuronal inhibition. Adverse side effects include sedation, dizziness, ataxia, anorexia, and behavioral disorders in children and manic responses in adults. Nephrolithiasis may occur in 3% of treated patients. Pharmacokinetic drug interactions are unlikely as zonisamide does not displace other drugs from protein binding sites and effects on metabolism of other drugs is minimal.

Benzodiazepines

Benzodiazepines display anxiolytic, sedative, muscle-relaxant, and anticonvulsant effects (see [Chapter 5](#)). Benzodiazepine receptors in the brain are a subset of GABA_A receptors. The binding of benzodiazepines to these receptors potentiates GABA-mediated neuronal inhibition, which increases chloride permeability and thereby leads to cellular hyperpolarization and inhibition of neuronal firing. In low doses, benzodiazepines suppress polysynaptic activity in the spinal cord and decrease neuronal activity in the mesencephalic reticular system.

Clonazepam

Clonazepam is generally added to other drug therapy and is used as a first-line drug only for myoclonic seizures.

Pharmacokinetics

Absorption of clonazepam after oral administration is rapid, with peak plasma concentrations occurring within 2 to 4 hours (see [Table 13.4](#)). An IV administration of clonazepam results in rapid CNS effects. Approximately 50% of the drug is bound to plasma proteins. Clonazepam is extensively metabolized to inactive products, with <2% of an injected dose appearing unchanged in urine. The elimination half-time of this long-acting drug is 30 to 40 hours. The oral maintenance dose is unlikely to exceed 0.25 mg/kg. Therapeutic plasma concentrations of clonazepam are 0.02 to 0.08 µg/mL.

Side Effects

Sedation is present in approximately 50% of patients but tends to subside with chronic administration (see [Table 13.3](#)). Skeletal muscle incoordination and ataxia occur in approximately 30% of patients. Personality changes occur in approximately 25% of patients, manifesting as behavioral disturbances, including hyperactivity, irritability, and difficulty in concentration, especially in children. Elderly patients treated with clonazepam may experience depression. Increased salivary and bronchial secretions may be particularly prominent in children. Generalized seizure activity may be precipitated if the drug is discontinued abruptly.

Diazepam

Diazepam is a mainstay for the treatment of status epilepticus and local anesthetic-induced seizures. The typical approach is administration of 0.1 mg/kg IV every 10 to 15 minutes until seizure activity has been suppressed or a maximum dose of 30 mg has been administered (see [Chapter 5](#)). Diazepam has a long elimination half-time of 27 to 48 hours. Metabolism of diazepam results in active metabolites.

Lorazepam

Lorazepam has a shorter elimination half-time (8-25 hours) than diazepam but a longer duration of antiepileptic action because it is not rapidly redistributed. Lorazepam is metabolized in the liver and has no active metabolites. Lorazepam, which is available in parenteral and oral formulations, is used to treat status epilepticus and as intermittent therapy for seizure clusters.

Clobazam

Clobazam is used for complex partial, tonic-clonic, and myoclonic seizures primarily as a second-line agent. It is metabolized in the liver and has an active metabolite and is excreted by the kidneys. The elimination half-life is 16 to 18 hours. Its potential for sedation, lethargy, and loss of therapeutic effect is significantly lower than other benzodiazepines. Like other drugs of this class, significant withdrawal may occur if discontinuation is not gradual.²⁴

Status Epilepticus

Status epilepticus is a medical emergency where the patient experiences prolonged or rapidly recurring convulsions for 5 minutes or more. The motor manifestations of convulsive status epilepticus may be symmetrical with tonic and then clonic activity. Rapid seizure control is associated with improved clinical outcome.²⁵

Treatment

Treatment begins with ensuring a patent upper airway and administration of oxygen. Maintenance of ventilation may require tracheal intubation. An IV access is obtained in anticipation of administering antiepileptic drugs. If hypoglycemia cannot be excluded, the patient is treated empirically with IV glucose (50 mL of 50% glucose for adults). Drug therapy of status epilepticus is typically with a benzodiazepine such as diazepam, lorazepam, or midazolam. In the absence of IV access, a rectal gel form of diazepam or an intranasal form of midazolam is available. Ventilatory depression necessitating support of ventilation may accompany administration of benzodiazepines. If benzodiazepines are not successful in extinguishing the seizure, other choices include fosphenytoin; phenytoin; phenobarbital; valproic acid; and continuous infusions of valproic acid, levetiracetam, and propofol. Hypotension and prolongation of the QT interval on the electrocardiogram may accompany administration of fosphenytoin necessitating a slowing in the rate of IV infusion.^{25,26}

Drugs Used for Treatment of Parkinson Disease

Parkinson disease affects 1% of the population, predominantly in those older than 60 years, although onset can occur significantly earlier. It is a chronically progressive neurodegenerative disease that results from the loss of dopaminergic neurons in the substantia nigra pars compacta region of the basal ganglia. The presence of Lewy bodies is also a consistent feature.²⁷ Dopamine is thought to act principally as an inhibitory neurotransmitter and acetylcholine as an excitatory neurotransmitter within the extrapyramidal system, and a proper balance is necessary for normal function. Approximately 80% of the dopamine in the brain is concentrated in the basal ganglia, mostly in the caudate nucleus and putamen. In patients with Parkinson disease, the basal ganglia content of dopamine may be as low as 10% of normal. As a result, an excess of excitatory cholinergic activity manifesting as progressive tremor, skeletal muscle rigidity, bradykinesia, and disturbances of posture results.

The objective in treating Parkinson disease is to treat debilitating symptoms. Currently all approved medications offer only palliative relief, as they do not affect progression of the disease. Often, combinations

of drugs with effects on the dopaminergic and cholinergic components of the extrapyramidal nervous system are used. Management decisions, including when to commence treatment, takes into account numerous factors including age, symptoms, stage of the disease, and the degree of interference with activities of daily living. Treatment strategies can be divided into those addressing motor symptoms, those addressing other adverse effects of the disease including nausea, depression, autonomic disturbances and cognitive impairment, and those addressing medication related side effects.²⁷ Failure of pharmacologic therapy is an indication for deep brain stimulation, with the primary targets being the globus pallidus internus or subthalamic nucleus.²⁸

Levodopa

Because dopamine does not readily cross the blood–brain barrier, the major approaches to therapy have involved the administration of its precursor, levodopa, or drugs that mimic the action of dopamine. Levodopa is the cornerstone of symptomatic therapy of Parkinson disease and its efficacy is unsurpassed even by newer drugs. Levodopa crosses the blood–brain barrier and is converted to dopamine by aromatic-L-amino-acid decarboxylase (dopa decarboxylase enzyme), acting to replenish dopamine stores in the basal ganglia. Levodopa is usually administered with a peripheral decarboxylase inhibitor (carbidopa or benserazide) to maximize entrance of this precursor into the brain before it is converted to dopamine. Furthermore, side effects associated with increased peripheral concentrations of dopamine are less when it is combined with a decarboxylase inhibitor. Absorption of levodopa from the gastrointestinal tract is efficient, but the brief elimination half-time (1-3 hours) requires frequent dosing intervals to maintain a therapeutic concentration. Recently, controlled release and extended release preparations has increased dosing intervals and reduced some side effects. An IV formulation of levodopa is not available.

The beneficial therapeutic response to levodopa typically diminishes after 5 to 10 years of treatment, presumably reflecting progression of the disease process and continuing loss of nigrostriatal neurons with a capacity to store dopamine. Abrupt discontinuation of levodopa therapy may result in a precipitous return of symptoms of Parkinson disease and has been associated with a neuroleptic malignant-like syndrome. For this reason, levodopa should be continued throughout the perioperative period.

Metabolism

Approximately 95% of orally administered levodopa is rapidly decarboxylated to dopamine during the initial passage through the liver. The resulting dopamine cannot easily cross the blood–brain barrier to exert beneficial effects, whereas increased plasma concentrations of dopamine often lead to undesirable side effects. In this regard, inhibition of the peripheral activity of the decarboxylase enzyme greatly increases the fraction of administered levodopa that remains intact to cross the blood–brain barrier.

At least 30 metabolites of levodopa have been identified. Most of these metabolites are converted to dopamine, small amounts of which are subsequently metabolized to norepinephrine and epinephrine. Metabolism of dopamine yields 3,4-dihydroxyphenylacetic acid (homovanillic acid). Dietary methionine is necessary as a source of methyl donors to permit continued activity of catechol-O-methyltransferase (COMT), which is necessary for the metabolism of the excess amounts of dopamine that result from high doses of levodopa. Most metabolites of dopamine are excreted by the kidneys.

Side Effects

The most common side effects that occur during the first weeks of therapy with levodopa and dopamine agonists are nausea and hypotension. These side effects are associated with peak plasma concentrations of dopamine and may be minimized by taking medications after light meals or snacks. The most common problems that occur during long-term therapy are dyskinesias, fluctuations in mobility, increasing confusion, and psychosis. These problems become progressively more frequent after the first 3 years of therapy.

Gastrointestinal Dysfunction

Nausea and vomiting occur in about 80% of patients during the early period of treatment with levodopa. These responses reflect dopamine-induced stimulation of the chemoreceptor trigger zone, which is not

protected by the blood–brain barrier.²⁹ Nausea can be effectively treated with domperidone, which does not easily cross the blood–brain barrier and is therefore unlikely to exacerbate symptoms of Parkinson disease. Domperidone inhibits dopamine-2 receptors in the chemoreceptor trigger zone of the medulla oblongata.³⁰ Trimethobenzamide can also be used and has a direct action on the chemoreceptor trigger zone and is devoid of dopaminergic action.³¹ Dopamine receptor antagonist antiemetics such as prochlorperazine, metoclopramide, and promethazine must be avoided because they significantly worsen symptoms of Parkinson disease. Gastrointestinal side effects tend to disappear with continuing therapy as tolerance develops.²⁷

Parkinsonism-Hyperpyrexia Syndrome

Sudden cessation or dose reduction of levodopa or dopamine antagonists may lead to a life-threatening emergency termed *parkinsonism-hyperpyrexia syndrome*. The clinical presentation is similar to neuroleptic malignant syndrome, with rigidity, pyrexia, autonomic instability, and a decreased level of consciousness. Potential complications include renal failure, aspiration pneumonia, deep venous thrombosis, pulmonary embolism, and death. Prompt recognition and management are imperative as this carries a 4% mortality rate. Treatment involves replacing Parkinson medications at the current dose. Levodopa can be given orally or, if necessary, by a nasogastric tube. A rotigotine patch or an apomorphine infusion can be commenced in an intensive care unit where careful observation for dysautonomia can be achieved along with supportive measures.³²

Cardiovascular Changes

Cardiovascular changes associated with levodopa most likely reflect α- and β-adrenergic responses evoked by increased plasma concentrations of dopamine and its metabolism to norepinephrine and epinephrine. Transient flushing of the skin is common during levodopa therapy.

Orthostatic Hypotension

Approximately 30% of patients develop orthostatic hypotension early in therapy. This can be due to autonomic dysfunction from the disease or as a result of levodopa treatment. It can be a significant problem in some patients and warrants continuous evaluation as it can result in syncopal episodes. Initial treatment consists of increased fluid and sodium intake, elevation of the head of the patient's bed, and compression stockings. If symptoms are persistent, administration of fludrocortisone, domperidone, or midodrine may be useful. Orthostatic hypotension becomes less prominent with continued therapy.^{27,29}

Cardiac Dysrhythmias

Cardiac dysrhythmias, including sinus tachycardia, atrial and ventricular premature contractions, atrial fibrillation, and ventricular tachycardia, although rare, have been associated with levodopa therapy. Presumably, the potential β-adrenergic effects of dopamine and its metabolites on the heart contribute to cardiac dysrhythmias, although a cause-and-effect relationship has not been documented. Patients with preexisting disturbances of cardiac conduction or coronary artery disease are most likely to develop cardiac dysrhythmias in association with levodopa therapy. Propranolol is an effective treatment when cardiac dysrhythmias occur in these patients.²⁹

Abnormal Involuntary Movements

Abnormal involuntary movements in the form of faciolingual tics; grimacing; and rocking movements of the arms, legs, or trunk are the most common side effects of chronic levodopa therapy, developing in about 50% of patients within 1 to 4 months after initiation of therapy. Rarely, exaggerated respiratory movements can produce an irregular gasping pattern, presumably reflecting dyskinesias of the diaphragm and intercostal muscles. Tolerance does not develop to abnormal involuntary movements.

Fluctuations in mobility are characterized by increasing bradykinesia at the end of an interval between doses. High-protein meals are avoided in patients who experience sudden loss of mobility because a large influx of dietary amino acids can interfere with the transport of levodopa into the brain.

Psychiatric Disturbances

Confusion, visual hallucinations, and paranoia may reflect the natural disease process as well as its treatment. Elderly patients are particularly vulnerable to psychotic reactions, especially if treatment includes combinations of levodopa and anticholinergic drugs and the patient has a prior psychiatric history. Psychiatric disturbances usually begin as nocturnal phenomena, emphasizing the possible value of decreasing or discontinuing the last evening dose of levodopa. Neuroleptic drugs are not recommended for the treatment of psychiatric disturbances because these drugs may cause a protracted exacerbation of symptoms of Parkinson disease. Quetiapine is a commonly prescribed medication as is clozapine. The routine laboratory monitoring with clozapine due to the risk agranulocytosis often makes quetiapine a more attractive option.²⁷ Patients who develop drug-induced psychosis with no features of dementia may respond to electroconvulsive therapy.

Impulsive and compulsive behavior may also result from dopaminergic therapy. A history of obsessive-compulsive disorder, addiction, or impulsive personality traits increases the likelihood. The development of these behaviors should be monitored regularly. Treatment is aimed at symptomatic relief primarily with dopamine agonists and less commonly with zonisamide, amantadine, topiramate, and valproate.^{27,33}

Endocrine Changes

Dopamine inhibits the secretion of prolactin, presumably by stimulating the release of a prolactin inhibitory factor. The release of growth hormone that occurs in response to the administration of levodopa to normal patients is minimal or absent when levodopa is administered to patients with Parkinson disease. Indeed, signs of acromegaly or diabetes mellitus do not occur in patients treated with levodopa. Large doses of levodopa may cause hypokalemia associated with increased plasma levels of aldosterone.

Laboratory Measurements

Urinary metabolites of levodopa cause false-positive tests for ketoacidosis. These metabolites also color the urine red and then black on exposure to air. Mild, transient increases in the blood urea nitrogen concentration may occur and can usually be controlled by increasing fluid intake. Increased liver transaminase concentrations occasionally occur. Positive Coombs tests have been attributed to levodopa.

Drug Interactions

Drug interactions may occur in patients being treated with levodopa, resulting in increased or decreased therapeutic effects. Chronic treatment of animals with levodopa does not consistently change anesthetic requirements.

Antipsychotic Drugs

Antipsychotic drugs such as butyrophenones and phenothiazines can antagonize the effects of dopamine. For this reason, these drugs should not be administered to patients with known or suspected Parkinson disease. Indeed, administration of droperidol to patients being treated with levodopa has produced severe skeletal muscle rigidity and even pulmonary edema, presumably reflecting sudden antagonism of dopamine. Droperidol has even produced a Parkinson disease–like syndrome in otherwise healthy patients. Metoclopramide may also interfere with dopamine activity.

Monoamine Oxidase Inhibitors

Nonspecific monoamine oxidase inhibitors interfere with the inactivation of catecholamines, including dopamine. As a result, these drugs can exaggerate the peripheral and CNS effects of levodopa. Hypertension and hyperthermia are side effects associated with the concurrent administration of these drugs.

Anticholinergic Drugs

Anticholinergic drugs act synergistically with levodopa to improve certain symptoms of Parkinson disease, especially tremor. Large doses of anticholinergics, however, can slow gastric emptying such that absorption of levodopa from the gastrointestinal tract is decreased.

Pyridoxine

Pyridoxine, in doses as low as 5 mg as present in multivitamin preparations, can abolish the therapeutic efficacy of levodopa by enhancing the activity of pyridoxine-dependent dopa decarboxylase and thus increasing the metabolism of levodopa in the circulation before it can enter the CNS.

Peripheral Decarboxylase Inhibitors

Levodopa is usually administered with a peripheral carboxylase inhibitor such as carbidopa or benserazide. As a result, more levodopa escapes metabolism to dopamine in the peripheral circulation and is available to enter the CNS. Furthermore, side effects related to high systemic concentrations of dopamine are decreased when levodopa is administered with a peripheral decarboxylase inhibitor. Nausea, vomiting, and cardiac dysrhythmias are diminished or absent. The incidence of abnormal involuntary movements and psychiatric disturbances is not altered by the combination of levodopa with a decarboxylase inhibitor.

Several combinations of levodopa and a peripheral carboxylase inhibitor are available as a levodopa augmentation strategy. Sinemet is composed of levodopa and carbidopa in a 10:1 or 4:1 ratio. Madopar is composed of levodopa and benserazide in a 4:1 ratio. Controlled-release preparations of levodopa and carbidopa provide a more constant therapeutic effect, but the onset of action is slower and the bioavailability is decreased compared with the standard combinations. Both carbidopa and benserazide are noncompetitive inhibitors of decarboxylase, so there is no value in administering progressively higher doses of these enzyme inhibitors. Carbidopa and benserazide do not cross the blood-brain barrier and lack pharmacologic activity when administered alone.

Catechol-O-methyltransferase Inhibitors

The COMT is partially responsible for the peripheral breakdown of levodopa. Accordingly, another levodopa augmentation strategy consists of blocking the COMT enzyme activity in the gastrointestinal tract with tolcapone or entacapone. Administration of either of these drugs slows the elimination of carbidopa-levodopa, thus increasing the plasma concentrations by 10% to 15%. In patients treated with tolcapone, the daily dose of carbidopa-levodopa may need to be decreased by 10% to 30% to avoid dyskinesias or other hyperdopaminergic side effects.

Side Effects

Both tolcapone and entacapone worsen levodopa-induced dyskinesias and cause nausea and diarrhea. Tolcapone may cause hepatotoxicity in rare patients emphasizing the need to monitor liver function tests in treated patients. Rhabdomyolysis has been associated with tolcapone therapy. Entacapone can cause the patient's urine to appear orange. Both drugs can cause piloerection.

Synthetic Dopamine Agonists

Synthetic dopamine agonists require neither transformation nor facilitated transport across the blood-brain barrier. Available drugs include the nonergot alkaloids pramipexole, ropinirole, and rotigotine as well as the tetracyclic ergot alkaloid bromocriptine, which is less commonly prescribed due to significant side effects. Pramipexole and ropinirole are oral preparations, which can be administered in an immediate- or extended-release fashion. Pramipexole and ropinirole may precipitate "sleep attacks," especially patients at higher doses. Factors that may increase the risk of experiencing these episodes include administration of sedatives and concurrent sleep disorders.³⁴ Rotigotine is a daily transdermal patch and is preferred by patients for convenience or due to an inability to swallow pills. After oral administration, the elimination half-time of bromocriptine is longer than for levodopa. Absorption of bromocriptine from the gastrointestinal tract is rapid but incomplete. Extensive hepatic first-pass metabolism occurs, and >90% of the metabolites are excreted in the bile, whereas <10% of the drug is excreted unchanged or as inactive metabolites in urine. Bromocriptine, 0.5 to 1.0 mg orally, is equivalent to levodopa, 100 mg in combination with either 25 mg of carbidopa or 25 mg of benserazide. The effectiveness of bromocriptine in the treatment of acromegaly reflects the paradoxical inhibitory effect of dopamine agonists on secretion of growth hormone. Bromocriptine also suppresses the

excess prolactin secretion that is often associated with growth hormone secretion. A notable benefit of rotigotine is its antidepressant effects.

Side Effects

Visual and auditory hallucinations, hypotension, and dyskinesia occur more frequently in patients treated with bromocriptine than in those treated with levodopa. Synthetic dopamine agonists occasionally cause pleuropulmonary fibrosis, sometimes with pleural effusions. Depending on the severity of this side effect, the dose of agonist drug should be decreased or the drug discontinued. Another uncommon complication of dopamine agonist therapy is the development of erythromelalgia (red, edematous, tender extremities). If this complication occurs, it is usually necessary to discontinue the dopamine agonist. Asymptomatic increases of serum transaminase and alkaline phosphatase concentrations may occur. Vertigo and nausea are occasionally associated with bromocriptine therapy.

Nonergot alkaloids are supposed to cause less nausea and orthostatic hypotension than the ergot derivatives, but this difference appears to be clinically insignificant. Nonergot alkaloids offer no advantage over ergot derivatives with respect to CNS side effects including confusion, hallucinations, and daytime sleep attacks that have been associated with motor vehicle accidents.

Dopamine agonists must not be stopped abruptly because it has been associated with a syndrome resembling neuroleptic malignant syndrome, and is termed *parkinsonism-hyperpyrexia syndrome* (discussed previously in this chapter under “[Side Effects](#)” in “[Levodopa](#)” section).

Anticholinergic Drugs

Anticholinergic drugs such as trihexyphenidyl and benztropine have modest effects on the clinical manifestations of Parkinson disease and are primarily used as a treatment for tremor. These drugs blunt the effects of the excitatory neurotransmitter acetylcholine, thus correcting the balance between dopamine and acetylcholine that is disturbed in the direction of cholinergic dominance. Anticholinergic drugs may help control the tremor and decrease the excess salivation associated with Parkinson disease but seldom are useful for skeletal muscle rigidity and bradykinesia. Although the peripheral and CNS actions of these synthetic anticholinergic drugs are less prominent than those of atropine, side effects, including memory disturbances (especially in elderly patients), hallucinations, confusion, sedation, mydriasis, cycloplegia, adynamic ileus, and urinary retention, may still occur. The mydriatic effect could precipitate glaucoma in a susceptible patient. As more effective drugs have become available, the use of anticholinergic drugs to treat patients with Parkinson disease has diminished.

Amantadine

Amantadine is an antiviral drug used for prophylaxis against infection with influenza A virus. This drug was discovered by chance to also produce symptomatic improvement in patients with Parkinson disease. The mode of action of amantadine is not known, although it has been speculated that it facilitates the release of dopamine from dopaminergic terminals that remain in the nigrostriatal pathway of patients with this disease. In addition, amantadine may delay uptake of dopamine back into nerve endings, exert anticholinergic effects, is a weak glutamate antagonist, and exhibits noncompetitive antagonist effects at *N*-methyl-D-aspartate receptors. Unlike anticholinergic drugs, amantadine may result in some improvement in skeletal muscle rigidity and bradykinesia. Amantadine is well absorbed after oral administration, and the elimination half-time is approximately 12 hours. More than 90% of the drug is excreted unchanged by the kidneys, necessitating dosage adjustments in patients with renal dysfunction. The side effects are similar to those produced by anticholinergic drugs, but, in addition, chronic administration of amantadine tends to induce ankle edema and livedo reticularis of the legs with or without cardiac failure. In older patients, amantadine may aggravate confusion and psychosis.

Monoamine Oxidase Type B Enzyme Inhibitors

This category comprises three drugs; selegiline, rasagiline, and safinamide. These drugs are believed to be of similar efficacy, and choice among them is based on preference of the clinician and/or patient. Selegiline is a

highly selective and irreversible inhibitor of monoamine oxidase type B (MAO-B) enzyme that has a weak antiparkinsonian effect when used alone and a moderate effect when used as an adjunct to carbidopa-levodopa. The MAO-B enzyme activity is one of the principal catabolic pathways for dopamine in the CNS. Blocking MAO-B enzyme activity increases the intrasynaptic half-time of dopamine leading to improved motor fluctuations and tremor. In contrast to nonspecific monoamine oxidase inhibitors, selegiline does not result in life-threatening potentiation of the effects of catecholamines when administered concurrently with a centrally active amine. This reflects the fact that metabolism of norepinephrine in peripheral nerve endings is not altered by selegiline, which minimizes the likelihood of adverse responses during anesthesia in response to sympathomimetics. Insomnia is a significant side effect of selegiline. Other side effects of selegiline include confusion, hallucinations, mental depression, and paranoid ideation.

Rasagiline has created enthusiasm as a potentially neuroprotective agent, but this activity requires further evaluation.³⁵ It has action at both the MAO-A and MAO-B enzyme, but its affinity is up to 16 times greater for MAO-B enzyme. It is recommended both as monotherapy and adjunctive therapy.³⁶ Although a theoretical risk does exist for the precipitation of serotonin syndrome, this was not observed during clinical trials. Similarly, avoidance of tyramine is ideally recommended, although no adverse reactions have been noted.³⁷

Safinamide is a selective, reversible MAO-B inhibitor with both dopaminergic and glutaminergic properties. It is prescribed for patients in mid- to late-stage Parkinson disease as add-on therapy to a levodopa to reduce “off” episodes. It is rapidly absorbed in the gastrointestinal system and reaches peak plasma concentrations in 2 to 3 hours. Similar to rasagiline, there is a theoretical risk for the precipitation of serotonin syndrome, and avoidance of tyramine is recommended.^{38,39}

Nonpharmacologic Treatment

Deep brain stimulation was approved to treat Parkinson disease by the U.S. Food and Drug Administration in 2002. Although not curative, it effectively controls symptoms resistant to medications or allows reduced reliance on drugs whose side effects have proven problematic. The mechanism of action of deep brain stimulation is unknown.²⁸ Other potential therapies under investigation include stem cell transplantation as well as transplantation of fetal mesencephalic tissue.

Central Nervous System Stimulants

Analeptics are drugs that stimulate the CNS. These drugs were previously used in the treatment of generalized CNS depression accompanying deliberate drug overdoses, but this practice has been abandoned because these drugs lack specific antagonist properties and their margin of safety is narrow. The excitability of the CNS reflects a balance between excitatory and inhibitory influences that is normally maintained within relatively narrow limits. Analeptics can increase excitability either by blocking inhibition or by enhancing excitation.

Amphetamine

Amphetamine is an analeptic prescribed primarily for attention deficit hyperactivity disorder, narcolepsy, and obesity. It is also used recreationally at much larger doses due to the intense euphoria, which may be experienced. Amphetamine salts are nonsympathetic amines, which exert a powerful stimulant effect. Amphetamine stimulates release of norepinephrine from central and peripheral nerve terminals. Physiologically, central effects include stimulation of respiratory centers, increased alertness, diminished fatigue, increased muscle strength, euphoria, and improved concentration. Peripherally, increased systolic and diastolic blood pressure, tachycardia or a reflex bradycardia, as well as a weak bronchodilator effect is observed.^{40,41}

Oral amphetamine preparations are well absorbed in the gastrointestinal tract, with increased absorption in higher gastric pH ranges. Oral bioavailability is 70% to 80%, and 30% to 40% is protein bound. The plasma half-life is dependent on urine pH; in a normal pH range, the half-life of most preparations is 10 to 15 hours, but in acidic urine, it is reduced to 5 to 10 hours. Amphetamines are metabolized in the liver. Alkaline

urine may extend the plasma half-life to 30 to 40 hours. Amphetamines are excreted by the kidneys, up to 50% unchanged.^{40,41}

The pattern of use of amphetamine has major impact on the anesthetic care of patients. Acute intoxication with amphetamine increases MAC, and chronic exposure decreases MAC. Chronic exposure, which causes continued stimulation of central and peripheral nerve terminals, results in depleted catecholamine receptor reserves. This is especially relevant during general anesthesia where a blunted physiologic response to hypotension may be observed, which may cause critical hemodynamic instability and critically decreased organ perfusion. Direct-acting vasopressors, which do not act via release of stored synaptic catecholamines, such as epinephrine, phenylephrine, or vasopressin, are the treatment of choice. Although it is recommended that surgery be delayed in all but emergent cases in a patient who is acutely intoxicated with amphetamine, the evidence for withholding chronic prescription stimulant is less clear, and it may be reasonable to continue them through the perioperative period.⁴²

Doxapram

Doxapram is an analeptic that acts centrally and at peripheral chemoreceptors to augment breathing efforts. The stimulus to ventilation produced by administration of doxapram, 1 mg/kg IV, is similar to that produced by a PaO₂ of 38 mm Hg acting on the carotid bodies. An increase in tidal volume, more than an increase in breathing frequency, is responsible for the doxapram-induced increase in minute ventilation. Oxygen consumption is increased concomitantly with the increase in minute ventilation.

Doxapram has a large margin of safety as reflected by a 20- to 40-fold difference in the dose that stimulates ventilation and the dose that produces seizures. Nevertheless, continuous infusion of doxapram, as is required to produce a sustained effect on ventilation, often results in evidence of subconvulsive CNS stimulation (hypertension, tachycardia, cardiac dysrhythmias, vomiting, and increased body temperature). These changes are consistent with increased sympathetic nervous system outflow. Continuous infusion is also required because the duration of action of a single IV dose is relatively short at 5 to 10 minutes. It is metabolized extensively, and less than 5% is excreted unchanged in the urine.

Clinical Uses

Doxapram administered as a continuous infusion (2-3 mg per minute) has been used as a temporary measure to maintain ventilation during administration of supplemental oxygen to patients with chronic obstructive airway disease who otherwise depend on a hypoxic drive to maintain adequate minute ventilation. Its role in the postoperative period has been used in preventing the ventilatory depression produced by opioids without altering analgesia. It has also been shown to be useful in treating postoperative shivering. Its use with apneic neonates in intensive care units can often delay or prevent intubation and ventilation, thus reducing ventilator-associated morbidity and mortality.

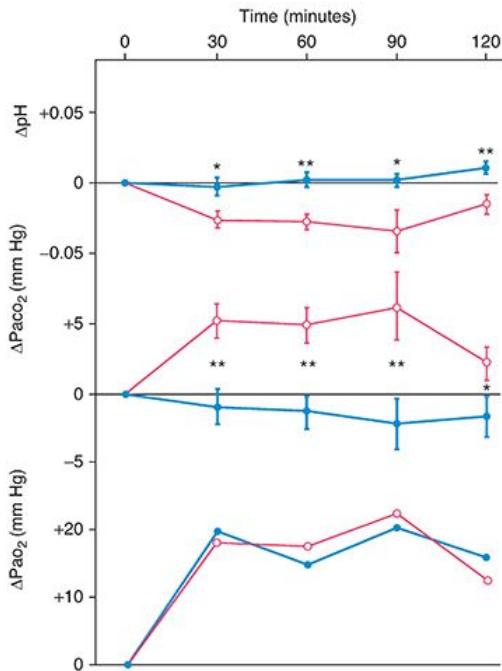


FIGURE 13.1 Doxapram, as a continuous infusion (solid circles), may be used to maintain alveolar ventilation during administration of supplemental oxygen to patients with chronic obstructive airway disease. The open circles represent placebo (* $P < .05$ compared with placebo infusion; ** $P < .01$ compared with placebo infusion). From Moser KM, Luchsinger PC, Adamson JS, et al. Respiratory stimulation with intravenous doxapram in respiratory failure. A double-blind co-operative study. N Engl J Med. 1973;288(9):427-431. Copyright © 1973 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Methylphenidate

Methylphenidate is a mild CNS stimulant structurally related to amphetamine. Absorption after oral administration is rapid, and its low protein binding and high lipid solubility results in rapid uptake into the brain. Methylphenidate is useful in the treatment of attention deficit hyperactivity disorder in children and adults.⁴³ Hypertension, tachycardia, priapism, seizures, and serious cardiovascular events such as sudden cardiac death, stroke, and myocardial infarction have been described in patients treated with methylphenidate. Methylphenidate may also be effective in the treatment of narcolepsy, either alone or in combination with tricyclic antidepressants.⁴⁴

Methylxanthines

Methylxanthines are represented by caffeine, theophylline, and theobromine. Solubility of methylxanthines is low and is enhanced by formation of complexes as represented by the combination of theophylline with ethylenediamine to form aminophylline. Methylxanthines have in common the ability to (1) stimulate the CNS, (2) produce diuresis, (3) increase myocardial contractility, and (4) relax smooth muscle, especially those in the airways.

Mechanism of Action

The best characterized cellular action of methylxanthines is antagonism of receptor-mediated actions of adenosine, thus facilitating the release of catecholamines. Theophylline is more active than caffeine or theobromine as an antagonist at these receptors. At high concentrations, theophylline inhibits phosphodiesterase enzymes that are responsible for breakdown of cyclic adenosine monophosphate. Methylxanthines are completely absorbed after oral administration and eliminated primarily by metabolism in

the liver. Unlike adults, premature infants metabolize theophylline in part to caffeine. Furthermore, the clearance of methylxanthines is greatly prolonged in the neonate compared with that in the adult.

Clinical Uses

Methylxanthines are used as analeptics to treat primary apnea of prematurity by stimulating medullary respiratory centers by increasing the sensitivity of these centers to carbon dioxide. The slowed metabolism of methylxanthines in neonates compared to adults is a consideration when using theophylline to stimulate ventilation in neonates. Smooth muscle relaxation and bronchodilation produced by theophylline may reflect a combination of effects including catecholamine release, phosphodiesterase inhibition, and inhibition of inflammation. The administration of theophylline during maintenance of anesthesia appears to have no added bronchodilator effect over that of the volatile anesthetic alone. Selective β_2 -adrenergic agonists delivered by inhalation have largely replaced theophylline preparations in the treatment of bronchospasm associated with asthma.

Toxicity

A single oral dose of theophylline, 5 mg/kg, will produce a peak plasma concentration of 10 $\mu\text{g}/\text{mL}$ in adults within 1 to 2 hours following ingestion. Increased levels of unbound drug may result in signs of toxicity despite therapeutic plasma concentrations of drug (10-20 $\mu\text{g}/\text{mL}$). Theophylline plasma concentrations only slightly greater than the recommended therapeutic range can produce evidence of CNS stimulation (nervousness, tremors) and at higher concentrations or with rapid IV administration seizures are a possibility. Vomiting most likely reflecting CNS stimulation is common when plasma concentrations exceed 15 $\mu\text{g}/\text{mL}$. Tachycardia and cardiac dysrhythmias may appear most likely due to drug-induced release of catecholamines from the adrenal medulla.

Drug Interactions

Drugs may enhance (carbamazepine, rifampin) or inhibit (cimetidine, erythromycin) the hepatic metabolism of theophylline. Larger doses of benzodiazepines may be required in the presence of theophylline as benzodiazepines increase the CNS concentrations of adenosine, a potent CNS depressant, whereas theophylline is an adenosine receptor antagonist. Ketamine may decrease the seizure threshold for theophylline. Theophylline can partially antagonize the effects of nondepolarizing neuromuscular-blocking drugs presumably by inhibition of phosphodiesterase.

Caffeine

Caffeine is a methylxanthine-derived phosphodiesterase inhibitor that is present in a variety of beverages and nonprescription medications. A prominent effect of caffeine is CNS stimulation. In addition, this substance acts as a cerebral vasoconstrictor and may cause secretion of acidic gastric fluid.

Pharmacologic uses of caffeine include administration to neonates experiencing apnea of prematurity.⁴⁵ Treatment of postdural puncture headache has historically been treated with doses ranging from 75 to 300 mg oral caffeine. Despite the limited evidence for this treatment, it continues to be a popular treatment modality.⁴⁶⁻⁴⁸ Caffeine may be included in common cold remedies in an attempt to offset the sedating effects of certain antihistamines.⁴⁹

Almitrine

Almitrine acts on the carotid body chemoreceptors to increase minute ventilation. It has been demonstrated to increase PaO_2 and decrease PaCO_2 in patients with chronic respiratory failure associated with obstructive pulmonary disease. Its mechanism of action has not been elucidated.⁵⁰ It is used as a measure to improve or prevent hypoxia during one-lung ventilation techniques, especially with IV anesthesia techniques.^{51,52} An IV administration of almitrine not only improves PaO_2 in patients with acute lung injury but may also induce lactic acidosis and hepatic dysfunction.⁵³ Side effects of prolonged oral almitrine therapy include dyspnea and peripheral neuropathy that significantly limits its use.⁵⁴

Modafinil

Modafinil is a wakefulness-promoting drug approved for patients with excessive daytime sleepiness associated with narcolepsy, obstructive sleep apnea, and shiftwork sleep disorder.^{55,56} In addition, it may result in euphoria as well as alteration in mood, affect, and thinking. Its mechanism of action is unknown. Its absorption is rapid, and peak plasma concentrations are reached after 4 hours. It undergoes hepatic metabolism, and its inactive metabolites are excreted by the kidneys. A feeling of fatigue and sedation following recovery from general anesthesia may be countered by administration of modafinil.⁵⁶

Centrally Acting Muscle Relaxants

The primary indication for centrally acting muscle relaxants is spasticity, which may accompany pathologic conditions such as stroke, cerebral palsy, multiple sclerosis, amyotrophic lateral sclerosis, and injuries to the CNS. They act directly on the CNS or on skeletal muscles to relieve spasticity. Spasticity of skeletal muscles occurs when there is an abnormal increase in resistance to passive movement of a skeletal muscle group because of hyperactive proprioceptive or stretch reflexes.

Baclofen

Baclofen is the chlorophenol derivative of GABA that acts as an agonist at GABA_B receptors in the dorsal horn of the spinal cord and is often administered for treatment of spastic hypertonia of cerebral and spinal cord origin. Baclofen relieves spasticity by activating G-protein linked presynaptic GABA_B receptors that hyperpolarize muscle spindle afferent neurons, thereby decreasing the number and amplitude of excitatory postsynaptic potentials along the dendrites of motor neurons. This drug has no effect on the neuromuscular junction. Baclofen is particularly effective in the treatment of flexor spasms and skeletal muscle rigidity associated with spinal cord injury or multiple sclerosis. Intrathecal administration of baclofen may be an effective treatment of spinal spasticity that has not responded to oral administration of the drug.

Baclofen is rapidly and almost completely absorbed from the gastrointestinal tract. The elimination half-time is 3 to 6 hours, with approximately 80% of the drug excreted unchanged in urine, emphasizing the need to modify the dose in patients with renal dysfunction. Therapeutic plasma concentrations are 80 to 400 mg/mL.

Use of baclofen is limited by its side effects, which include sedation, skeletal muscle weakness, and confusion. Sudden discontinuation of chronic baclofen therapy may result in severe withdrawal reactions including evidence of multiple organ system failure, tachycardia, and both auditory and visual hallucinations. A case report of cardiac arrest due to baclofen withdrawal has been reported. Vocal cord spasm has been described following abrupt discontinuation of an intrathecal baclofen infusion. Coma, depression of ventilation, and seizures may accompany an overdose of baclofen. The threshold for initiation of seizures may be lowered in patients with epilepsy. Mild hypotension may occur in awake patients being treated with oral baclofen, whereas bradycardia, hypotension, and delayed awakening have been observed when general anesthesia is induced in these patients. Hemodynamic instability and delayed awakening following general anesthesia have been described in a patient receiving an accidental intrathecal overdose of baclofen. A decrease in sympathetic nervous system outflow from the CNS mediated by a GABA-baclofen-sensitive system might contribute to this hemodynamic response. Rarely, increases in liver transaminases and blood glucose levels have occurred.

Benzodiazepines

Benzodiazepines are widely used as centrally acting skeletal muscle relaxants. Diazepam is the most widely prescribed of this class, followed by clonazepam. These drugs are particularly beneficial for spinal spasticity and have little effect on cerebral spasticity. Sedation may limit the efficacy of these drugs as muscle relaxants but may be useful for relief of spasms that limit sleep.⁵⁷

Botulinum Toxin

Botulinum toxin causes irreversible inhibition of presynaptic acetylcholine release. Injections are made into spastic muscles, thereby causing weakening of muscle tone. Botulinum toxin is used in cases of central or

peripheral spasticity, particularly when limited muscle groups are affected. It has been used for spasticity and to prevent contractures in cerebral palsy, multiple sclerosis, and after stroke. Focally, it can be used for blepharospasm, hemifacial spasm, and torticollis.⁵⁸

Cyclobenzaprine is related structurally and pharmacologically to the tricyclic antidepressants. Its anticholinergic effects are similar to those of tricyclic antidepressants and can include dry mouth, tachycardia, blurred vision, and sedation. The mechanism of skeletal muscle relaxant effects produced by cyclobenzaprine is unknown. It must not be administered in the presence of monoamine oxidase inhibitors. In view of the potential adverse side effects of some tricyclic antidepressant drugs on the heart, the use of cyclobenzaprine may be questionable in patients with cardiac dysrhythmias or altered conduction of cardiac impulses.

Tizanidine

Tizanidine is a short-acting α_2 -adrenergic agonist whose structure is similar to clonidine. It reaches peak plasma levels at 2 hours after administration, and its clinical effect lasts only 6 hours, which necessitates repeated dosing if needed. Its absorption is highly variable depending on whether the patient has recently eaten or is fasted. Dosage adjustments must be made in patients with renal and hepatic dysfunction. Significant side effects include hypotension and care must be taken with patients who take antihypertensive agents. Significant sedation can also result, and there is an additive effect with other sedatives such as benzodiazepines. Discontinuation of therapy should be gradual as not to precipitate rebound hypertension, tachycardia, and/or hypertonia.

Dantrolene

Dantrolene exerts antispasmodic effects by inducing relaxation directly on muscle by decreasing calcium release from the sarcoplasmic reticulum. Its absorption from the gastrointestinal tract is slow and incomplete, and its half-life is 9 hours. The starting dose is usually 25 mg twice daily, and dosage can be increased up to 200 mg per day. Laboratory investigation for liver dysfunction should be undertaken prior to starting therapy as there is potential for hepatotoxicity especially in those patients with preexisting hepatic compromise.

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PART III Circulatory System

Circulatory Physiology*

Updated by: James Ramsay

Systemic Circulation

The systemic circulation supplies blood to all the tissues of the body including the lungs via the bronchial circulation. Important considerations in understanding the physiology of the systemic circulation include the anatomic components of the systemic circulation, physical characteristics of the systemic circulation and of blood, determinants and control of tissue blood flow, regulation of systemic blood pressure, and regulation of cardiac output and venous return. In addition, the fetal circulation possesses many unique features, which distinguish it from the systemic circulation after birth (see [Chapter 45](#)).

Endothelial Function

The entire vascular system is lined by endothelial cells. Thus, the endothelium is a large and widely distributed structure. Indeed, it is estimated that the adult endothelium is composed of 10 trillion cells and weighs approximately 1 kg.¹ It is now widely appreciated that the endothelium is not simply an inert lining layer of the circulation but is an important “organ” that is involved in many physiologic processes in health and disease ([Tables 14.1](#) and [14.2](#)). The luminal side of the endothelium is lined with a “glycocalyx,” a web of membrane-bound glycoproteins and proteoglycans, which plays an important role in transcapillary flow.² The healthy endothelium promotes vasodilation and confers antithrombotic and antiadhesive properties to the vessel wall; damages to the glycocalyx and endothelium result in increased vascular permeability and adherence of inflammatory mediators and cells. The endothelium also regulates smooth muscle proliferation and has an important role in the regulation of glucose and lipid metabolism. Endothelial dysfunction is an important element of cardiovascular disease and aging. Cardiovascular risk factors including smoking, diabetes mellitus, hyperlipidemia, obesity, and systemic hypertension are related to their adverse effects upon endothelial function.

TABLE 14.1

Physiologic roles of endothelial function

Endothelial function	Example
Regulation of vascular tone	Vasodilator release (nitric oxide, prostacyclin) Vasoconstrictor release (thromboxane A ₂ , leukotriene, endothelia, angiotensin-converting enzyme)
Regulation of coagulation	Procoagulant release Anticoagulant release
Vascular growth regulation (angiogenesis)	Growth factor synthesis and release
Lipid clearance	LDL receptor expression Lipoprotein lipase synthesis
Inflammatory regulation and defense	Inflammatory mediator synthesis and release
Vascular support matrix elaboration	Synthesis of collagen, laminin, fibronectin, proteoglycans, proteases
Regulation of molecular transport	Transport of glucose, amino acid, and albumin

Abbreviation: LDL, low-density lipoprotein.

TABLE 14.2**Pathologic processes associated with endothelial dysfunction**

Systemic hypertension

Pulmonary hypertension

Atherosclerosis

Sepsis and inflammation

Multisystem organ failure

Metastatic tumor spread

Thrombotic disorders

Endothelial Function and Regulation of Vascular Tone

Endothelial synthesis and release of vasoactive mediators are important elements in the regulation of vascular tone. Substances are released by the endothelium in response to both mechanical and humoral stimuli and generally have an immediate effect on the adjacent vascular smooth muscle tone. However, there may also be endothelium-induced long-term effects from vascular remodeling and smooth muscle hypertrophy. Under physiologic conditions, local vascular pressure and flow are the primary stimuli for endothelial vasoactive substance release. Nitric oxide (NO) and prostacyclin are powerful vasodilators released by endothelial cells and both also inhibit platelet aggregation and thrombosis. Continuous NO production maintains vascular tone in a normally low state. This minute-to-minute regulation of local vascular tone is controlled by type 3 constitutive NO synthase (cNOS). The cNOS is a rapidly responding endothelial enzyme that catalyzes the local conversion of L-arginine into small quantities of NO in response to endothelial shear stress during normal pulsatile flow. On the other hand, type 2 inducible NOS (iNOS) is a relatively slow-responding enzyme that catalyzes the production of large amounts of NO in response to inflammatory cytokines. The widespread generation of large amounts of NO via iNOS is responsible for the low systemic vascular resistance and hypotension encountered in septic shock.³ Endothelin-1 (ET-1) is a potent vasoactive compound released by the endothelium. Its predominant effect is vasoconstriction via smooth muscle ET_A receptors. However, ET-1 can also cause vasodilation through its effect on endothelial ET_B receptors. The ET-1 stimulates smooth muscle proliferation and is an important factor in the development of vascular structural changes in systemic and pulmonary hypertension.

Components of the Systemic Circulation

The components of the systemic circulation are the arteries, arterioles, capillaries, venules, and veins.

Arteries

The function of the arteries is to transport blood under high pressure to tissues. Therefore, arteries have strong vascular walls and blood flows rapidly through their lumens.

Arterioles

Arterioles are the last small branches of the arterial system, having diameters of less than 200 microns. Arterioles have strong muscular walls, which are capable of dilating or contracting and thus controlling blood flow into the capillaries. Indeed, blood flow to each tissue is controlled almost entirely by resistance to flow in the arterioles. Metarterioles arise at right angles from arterioles and branch several times, forming 10 to 100 capillaries which in turn connect with venules.

Capillaries

Capillaries are the sites for transfer of oxygen and nutrients to tissues and receipt of metabolic byproducts.

Venules and Veins

Venules collect blood from capillaries for delivery to veins, which act as conduits for transmitting blood to the right atrium. Because the pressure in the venous system is low, venous walls are thin. Nevertheless, walls of veins are muscular, which allows these vessels to contract or expand and thus store varying amounts of blood, depending on physiologic needs. As a result, veins serve an important storage function as well as being conduits to return blood to the right atrium. A venous pump mechanism is important for propelling blood forward to the heart.

Physical Characteristics of the Systemic Circulation

The systemic circulation contains about 80% of the blood volume, with the remainder present in the pulmonary circulation and heart (Figure 14.1).⁴ Of the blood volume in the systemic circulation, about 64% is in veins and 7% is in the cardiac chambers. The heart ejects blood intermittently into the aorta such that blood pressure in the aorta fluctuates between a systolic level of about 120 mm Hg and a diastolic level of about 80 mm Hg (Table 14.3; Figure 14.2).⁴

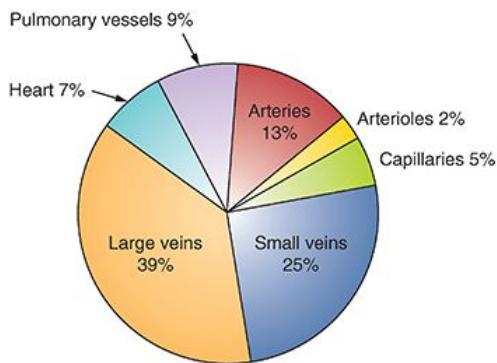


FIGURE 14.1 Distribution of blood volume in the systemic and pulmonary circulation. Reprinted from Guyton AC, Hall JE. Textbook of Medical Physiology. 10th ed. Philadelphia, PA: W.B. Saunders; 2000. Copyright © 2000 Elsevier. With permission.

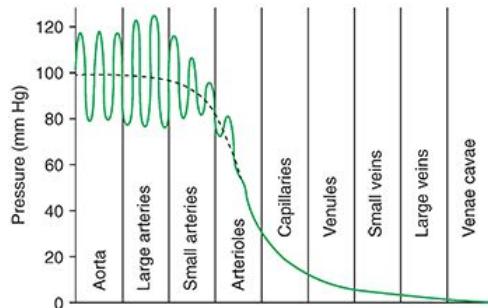


FIGURE 14.2 Systemic blood pressure decreases as blood travels from the aorta to large veins. Reprinted from Guyton AC, Hall JE. Textbook of Medical Physiology. 10th ed. Philadelphia, PA: W.B. Saunders; 2000. Copyright © 2000 Elsevier. With permission.

TABLE 14.3

Normal pressures in the systemic circulation

	Mean value (mm Hg)	Range (mm Hg)
Systolic blood pressure ^a	120	90-140
Diastolic blood pressure ^a	80	70-90
Mean arterial pressure	92	77-97

Left ventricular end diastolic pressure	6	0-12
Left atrium		
a Wave	10	2-12
v Wave	13	6-20
Right atrium		
a Wave	6	2-10
c Wave	5	2-10
v Wave	3	0-8

^aMeasured in the radial artery.

One of the primary responsibilities of the anesthesiologist is to maintain organ perfusion with oxygenated blood. Our standard physiologic monitors (heart rate, blood pressure, pulse oximetry, capnography) all serve as surrogate markers of organ perfusion and oxygenation. Currently, our standard monitoring techniques do not allow us to directly monitor the level of perfusion in specific organs or tissues. However, various techniques for monitoring end-organ perfusion are being explored and will likely be increasingly used in the years to come.

Measurement of Systemic Blood Pressure

Measurement of Blood Pressure by Auscultation

Measurement of blood pressure by auscultation uses the principle that blood flow in large arteries is laminar and not audible. If blood flow is arrested by an inflated cuff and the pressure in the cuff is released slowly, audible tapping sounds (Korotkoff sounds) can be heard when the pressure of the cuff decreases just below systolic blood pressure and blood starts flowing in the brachial artery. These tapping sounds occur because flow velocity through the constricted portion of the blood vessel is increased, resulting in turbulence and vibrations that are heard through the stethoscope. Diastolic blood pressure correlates with the onset of muffled auscultatory sounds. The auscultatory method for determining systolic and diastolic blood pressure usually gives values within 10% of those determined by direct measurement from the arteries.

The width of the blood pressure cuff will affect measurements; ideally, the width of the blood pressure cuff should be 20% to 50% greater than the diameter of the patient's extremity. If the cuff is too narrow, the blood pressure will be overestimated. If the cuff is too large, the blood pressure may be underestimated.

Direct Measurement of Blood Pressure With an Intravascular Catheter

In the operating room and intensive care unit, intravascular pressure is measured using an electronic transducer attached to tubing which is in turn connected to a catheter in the blood vessel, for example, a catheter in the radial artery. The transducer is then "zeroed" and "leveled" such that zero is the pressure when the transducer is open to air, and it is placed at the level of the heart (see later under "[Measuring Central Venous Pressure](#)"). The arterial waveform maybe "underdamped," meaning the catheter-transducer system overestimates the systolic pressure due to amplification of the pressure wave, or "overdamped," where the systolic pressure underestimated, usually due to air bubbles in the system or some kind of obstruction at the catheter tip. It is worthwhile to remember that the world literature on blood pressure is almost entirely based on noninvasive measurement (ie, auscultation), and direct measurement does not always give the same numbers.

Progressive Declines in Systemic Blood Pressure

As blood flows through the systemic circulation, perfusion pressure decreases progressively to nearly 0 mm Hg by the time blood reaches the right atrium (see [Figure 14.2](#)).⁴ The decrease in systemic blood pressure in each portion of the systemic circulation is directly proportional to the resistance to flow in the vessels. Resistance to blood flow in the aorta is minimal, and mean arterial pressure decreases only 3 to 5 mm Hg as blood travels into arteries as small as 3 mm in diameter. Resistance to blood flow begins to increase rapidly in small arteries, causing the mean arterial pressure to decrease to about 85 mm Hg at the beginning of the

arterioles. It is in the arterioles that resistance to blood flow is the highest, accounting for about 50% of the resistance in the entire systemic circulation. As a result, systemic blood pressure decreases to about 30 mm Hg at the point where blood enters the capillaries. At the venous end of the capillaries, the intravascular pressure has decreased to about 10 mm Hg. The decrease in systemic blood pressure from 10 mm Hg to nearly 0 mm Hg as blood traverses veins indicates that these vessels impart far more resistance to blood flow than would be expected for vessels of their large sizes. This resistance to blood flow is caused by compression of the veins by external forces that keep many of them, especially the vena cava, partially collapsed.

Pulse Pressure in Arteries

Pulse pressure reflects the intermittent ejection of blood into the aorta by the heart (see [Table 14.3](#)). The difference between systolic and diastolic blood pressure is the pulse pressure. A typical systemic blood pressure curve recorded from a large artery is characterized by a rapid increase in pressure during ventricular systole followed by a maintained high level of blood pressure for 0.2 to 0.3 second ([Figure 14.3](#)). This plateau is followed by the dicrotic notch (incisura) at the end of systole and a subsequent, more gradual decrease of pressure back to the diastolic level. The dicrotic notch reflects a decrease in the intraventricular pressure and a backflow of blood in the aorta, which causes the aortic valve to close.

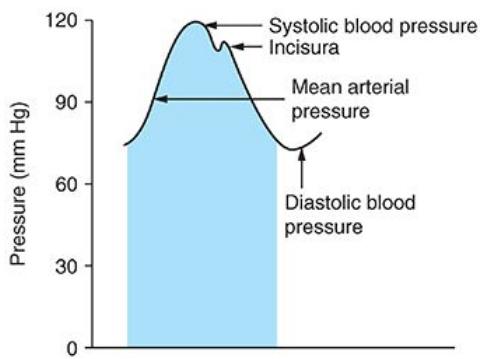


FIGURE 14.3 Schematic depiction of systemic blood pressure recorded from a large systemic artery. Mean arterial pressure is equal to the area under the blood pressure curve divided by the duration of systole.

Factors That Alter Pulse Pressure

The principal factors that alter pulse pressure in the arteries are the left ventricular stroke volume, velocity of blood flow, and compliance of the arterial tree. The larger the stroke volume, the greater the volume of blood that must be accommodated in the arterial vessels with each contraction resulting in an increased pulse pressure. Pulse pressure also increases when capacitance increases for outflow. When systemic vascular resistance decreases, flow of blood from arteries to veins is accelerated. Pulse pressure is also increased in the presence of patent ductus arteriosus and aortic regurgitation, reflecting rapid runoff of blood into the pulmonary circulation or left ventricle, respectively. In this regard, attempts have been made to predict systemic vascular resistance by the position of the dicrotic notch relative to the diastolic pressure. A controlled study, however, failed to confirm a correlation between the position of the dicrotic notch and the calculated systemic vascular resistance ([Figure 14.4](#)).⁵ An increase in heart rate while the cardiac output remains constant causes the stroke volume and pulse pressure to decrease. Pulse pressure is inversely proportional to the compliance (distensibility) of the arterial system. For example, with aging, the distensibility of the arterial walls often decreases (elastic and muscular tissues are replaced by fibrous tissue) and pulse pressure increases.

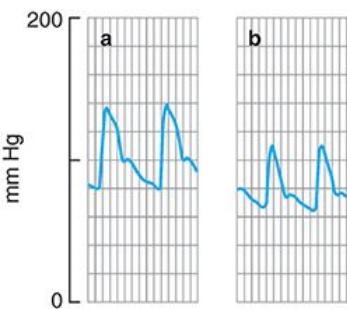


FIGURE 14.4 Despite a different height of the dicrotic notch (measured from baseline to the peak of the notch), the calculated systemic vascular resistance is similar for tracings a and b. *Reprinted with permission from Gerber MJ, Hines RL, Barash PG. Arterial waveforms and systemic vascular resistance: is there a correlation? Anesthesiology. 1987;66(6):823-825. Copyright © 1987 American Society of Anesthesiologists, Inc.*

Transmission of the Pulse Pressure

There is often enhancement of the pulse pressure as the pressure wave is transmitted peripherally ([Figure 14.5](#)).⁴ Part of this augmentation results from the progressive decrease in compliance of the more distal portions of the large arteries. Second, pressure waves are reflected to some extent by the peripheral arteries. Specifically, when a pulsatile pressure wave enters the peripheral arteries and distends them, the pressure on these peripheral arteries causes the pulse wave to begin traveling backward. If the returning pulse wave strikes an oncoming wave, the two summate, causing a much higher pressure than would otherwise occur.

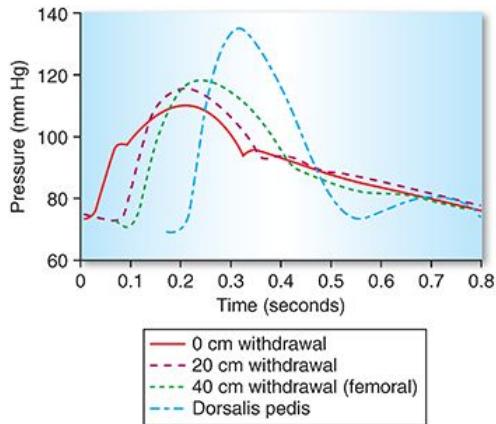


FIGURE 14.5 There is enhancement of the pulse pressure as the systemic blood pressure is transmitted peripherally. *From Guyton AC, Hall JE. Textbook of Medical Physiology. 10th ed. Philadelphia, PA: Saunders; 2000, with permission.*

These changes in the contour of the pulse wave are most pronounced in young patients, whereas in elderly patients with less compliant arteries, the pulse wave may be transmitted virtually unchanged from the aorta to peripheral arteries.

Augmentation of the peripheral pulse pressure must be identified whenever systemic blood pressure measurements are made in peripheral arteries. For example, systolic pressure in the radial artery is sometimes as much as 20% to 30% higher than that pressure present in the central aorta, and diastolic pressure is often decreased as much as 10% to 15%. Mean arterial pressures are similar regardless of the site of blood pressure measurement in a peripheral artery.

Pulse pressure becomes progressively less as blood passes through small arteries and arterioles until it becomes almost absent in capillaries (see [Figure 14.2](#)).⁴ This reflects the extreme distensibility of small vessels such that the small amount of blood that is caused to flow during a pulsatile pressure wave produces

progressively less pressure increase in the more distal vessels. Furthermore, resistance to blood flow in these small vessels is such that flow of blood and, consequently, the transmission of pressure are greatly impeded.

Systemic Blood Pressure Measurement During and After Cardiopulmonary Bypass

Reversal of the usual relationship between aortic and radial artery blood pressures can occur during the late period of hypothermic cardiopulmonary bypass and in the early period after termination of cardiopulmonary bypass ([Figure 14.6](#)).^{6,7} One mechanism proposed for this unpredictable and transient disparity (usually persists for 10-60 minutes after discontinuation of cardiopulmonary bypass) is a high blood flow in the forearm and hand after rewarming on cardiopulmonary bypass, causing an increased pressure drop along the normal resistance pathway provided by the arteries leading to the radial site. Conversely, others describe the appearance of this gradient with initiation of cardiopulmonary bypass, suggesting that the etiology is associated with events such as cross-clamping of the aorta occurring during initiation of cardiopulmonary bypass rather than rewarming or discontinuing cardiopulmonary bypass ([Figure 14.7](#)).^{8,9} Failure to recognize this disparity may lead to an erroneous diagnosis and unnecessary treatment. Systemic blood pressure measured in the brachial artery is more accurate and reliable during the periods surrounding cardiopulmonary bypass, which are most likely to be associated with disparities between the aortic and radial artery blood pressures.¹⁰

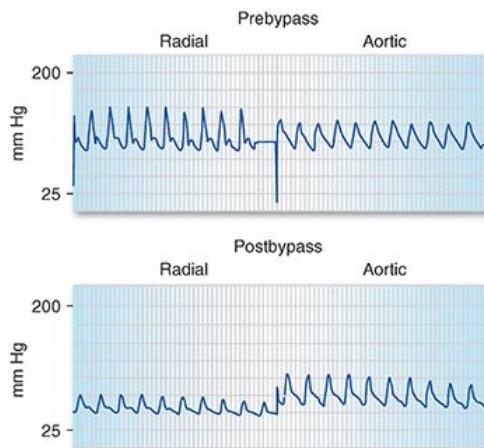


FIGURE 14.6 There may be a reversal of the usual relationship of simultaneous recordings of radial and aortic blood pressures (pre-bypass) in the early period after separation from cardiopulmonary bypass (post-bypass). Reprinted with permission from Stern DH, Gerson JI, Allen FB, et al. Can we trust the direct radial artery pressure immediately following cardiopulmonary bypass? *Anesthesiology*. 1985;62(2):557-561. Copyright © 1985 American Society of Anesthesiologists, Inc.

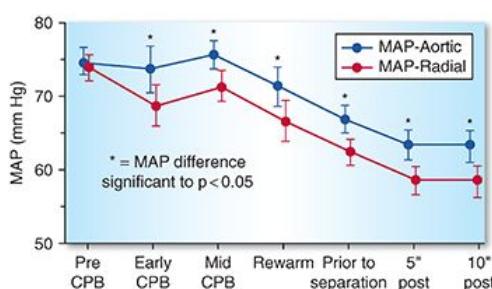


FIGURE 14.7 Comparison of mean arterial pressure (MAP) as measured from the aorta or radial artery before, during, and after cardiopulmonary bypass (CPB). Reprinted with permission from Rich GF, Lubanski RE Jr, McLoughlin TM. Differences between aortic and radial artery pressure associated with cardiopulmonary bypass. *Anesthesiology*. 1992;77(1):63-66. Copyright © 1992 American Society of Anesthesiologists, Inc.

Pulsus Paradoxus

Pulsus paradoxus is an exaggerated decrease in systolic blood pressure (>10 mm Hg) during inspiration in the presence of increased intrapericardial pressures (cardiac tamponade). During normal inspiration, the decrease in intrathoracic pressure increases the compliance of the pulmonary vasculature, which leads to a relative decrease in pulmonary venous return to the left ventricle. The resultant reduction in left ventricular preload decreases the stroke volume, which manifests as a mildly decreased systolic blood pressure during inspiration (<10 mm Hg). Cardiac tamponade causes an exaggeration of this change in blood pressure with respiration.

Pulsus Alternans

Pulsus alternans is alternating weak and strong cardiac contractions causing a similar alteration in the strength of the peripheral pulse. A variety of physiologic conditions are associated with pulsus alternans. Digitalis toxicity, varying degrees of atrioventricular heart block, and left ventricular dysfunction are commonly associated with pulsus alternans. In the setting of left ventricular dysfunction, pulsus alternans is caused by cyclic alterations in the contractile state of the heart. A reduced stroke volume increases end diastolic volume, which results in increased myocardial contraction and therefore increased ventricular emptying and blood pressure (per the Frank-Starling law). During the subsequent cardiac cycle, the lower filling pressures in the left ventricle result in a decreased stroke volume and therefore decreased ventricular emptying and blood pressure.

Electrical Alternans

Electrical alternans is a phenomenon where the amplitude of the QRS complex changes between heart beats. This electrocardiographic finding is seen in cardiac tamponade and pericardial effusion, where the heart essentially moves within the fluid-filled pericardial sac during contraction.

Pulse Deficit

In the presence of atrial fibrillation or ectopic ventricular beats, two beats of the heart may occur so close together that the ventricle does not fill adequately, and the second cardiac contraction ejects an insufficient volume of blood to create a peripheral pulse. In this circumstance, a second heart beat is audible with a stethoscope applied on the chest directly over the heart, but a corresponding pulsation in the radial artery cannot be palpated. This phenomenon is called a **pulse deficit**.

The Venous Circulation

Right Atrial Pressure

Right atrial pressure is regulated by a balance between venous return and the ability of the right ventricle to eject blood. Normal right atrial pressure is about 5 mm Hg, with a lower limit of about -5 mm Hg, which corresponds to the pressure in the pericardial and intrapleural spaces that surround the heart. Right atrial pressure approaches these low values when right ventricular contractility is increased or venous return to the heart is decreased by hemorrhage. Poor right ventricular contractility or any event that increases venous return (hypervolemia, venoconstriction) tends to increase right atrial pressure. Pressure in the right atrium is commonly designated the **central venous pressure** (CVP). Other factors that increase CVP include tension pneumothorax, heart failure, tamponade, pleural effusion, mechanical ventilation, positive end-expiratory pressure, Valsalva, pulmonary hypertension, and pulmonary embolism.

As the majority of the circulatory volume resides in the systemic veins, the function of the venous system (venous volume, capacitance, resistance, and venous return) is a major determinant of how much blood is pumped by the heart, or the cardiac output. Studies over the last 20 years have clearly shown that in the normal heart, measurement of CVP in response to physiologic challenges (position changes, leg raising, or fluid administration) is a much better indicator of adequacy of circulatory volume or “volume responsiveness” than isolated CVP measurement.¹¹ This is because of the many reflexes and physiologic

compensations in place, which maintain the venous return and filling of the right side of the heart. Exceptions to this principle include severe hypovolemia or hypervolemia where a very low CVP or high CVP likely confirms these states, respectively, and right ventricular dysfunction. Especially in the latter case, isolated CVP measurements can be a helpful indicator of the interaction between circulatory volume and how the right heart is dealing with it.

Measuring Central Venous Pressure

Critical to the interpretation of CVP (and other intravascular pressures) is accurate measurement. This is done with a transducer that is placed (“leveled”) to the tricuspid valve. From surface anatomy, this level or the “phlebostatic axis,” is typically at the fourth interspace in the midaxillary line. As the CVP is usually less than 10 mm Hg, small errors in the transducer level can make a big difference in clinical interpretation. Each centimeter below the hydrostatic point adds 0.77 mm Hg to the measured pressure, whereas 0.77 mm Hg is subtracted for each centimeter above this point. A pressure measurement in mm Hg can be converted to cm H₂O by multiplying the pressure by 1.36, which adjusts for the density of mercury relative to water (10 mm Hg equals 13.6 cm H₂O). Conversely, dividing the CVP measurement in cm H₂O by 1.36 converts this value to an equivalent pressure in mm Hg.

In the intensive care unit, transducers are usually affixed to the patient’s intravenous pole, and a spirit level mounted in a long ruler is used to confirm the transducer is at the phlebostatic axis when the pressure is measured. Another factor that can affect the measurement is patient position: If the patient is supine or up to approximately 30 degrees head up, the CVP is not affected, but if the patient is sitting up more than 45 degrees or is in the head-down position, the CVP will not be the same as in the 0- to 30-degree position. A general principle is to try to measure the CVP with the patient in the same position over time.

The reason for lack of hydrostatic effects at the tricuspid valve is the ability of the right ventricle to act as a regulator of pressure at this site. For example, if the pressure at the tricuspid valve increases, the right ventricle fills to a greater extent, thereby decreasing the pressure at the tricuspid valve toward normal. Conversely, if the pressure decreases at the tricuspid valve, the right ventricle does not fill optimally and blood pools in the veins until pressure at the tricuspid valve again increases to a normal value. In a poorly functioning right heart, these normal adaptations may not be able to be met and the patient’s position in bed may affect the CVP to a greater degree. The pressure measured at the fourth interspace in the midaxillary line may be significantly lower in the sitting position than in the supine position.

Jugular Venous Pressure

Jugular venous pressure or the pressure in the internal jugular vein mirrors the CVP. The normal jugular venous pressure reflects phasic changes in the right atrium and consists of three positive waves and three negative troughs ([Figure 14.8](#)).¹² Abnormalities of these venous waveforms may be useful in the diagnosis of various cardiac conditions ([Table 14.4](#)).¹²

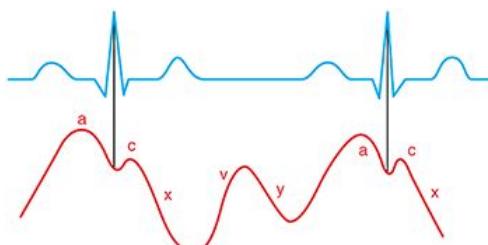


FIGURE 14.8 The jugular or central venous pressure waveform (lower tracing), aligned with the electrocardiogram (upper tracing). The physiologic events associated with the changes in waveform are as follows: *a* wave represents right atrial contraction, *c* wave represents tricuspid valve bulging into the atrium at the onset of ventricular systole, *x* descent represents right atrial relaxation, *v* wave represents rapid filling of the right atrium, and *Yy* descent represents early ventricular filling after opening of the tricuspid valve.

TABLE 14.4**Cardiac conditions associated with changes in central or jugular venous waveforms**

Sinus tachycardia	Reduced or absent <i>a</i> wave
Atrial fibrillation	Absent <i>a</i> wave
Atrial flutter	“Flutter <i>a</i> waves” without subsequent waves/descents
First-degree heart block	Prominent <i>a</i> waves
Tricuspid or pulmonic stenosis	Prominent <i>a</i> waves
Complete heart block	“Cannon” (very large) <i>a</i> waves
Tricuspid regurgitation	Absent <i>x</i> descent, large <i>c-v</i> waves, and rapid <i>y</i> descent
Constrictive pericarditis	Rapid <i>x</i> and <i>y</i> descents
Cardiac tamponade	Decreased <i>y</i> descent

Peripheral Venous Pressure

Large veins offer little resistance to blood flow when they are distended. Most large veins, however, are compressed at multiple extrathoracic sites. For example, pressure in the external jugular vein is often so low that atmospheric pressure on the outside of the neck causes it to collapse. Veins coursing through the abdomen are compressed by intra-abdominal pressure, which may increase 15 to 20 mm Hg as a result of pregnancy or ascites. When this occurs, pressure in leg veins must increase above abdominal pressure. It is important to recognize that veins inside the thorax are not collapsed because of the distending effect of negative intrathoracic pressure.

Effect of Hydrostatic Pressure

Pressure in veins below the heart is increased and that in veins above the heart is decreased by the effect of gravity ([Figure 14.9](#)).⁴ As a guideline, pressure changes 0.77 mm Hg for every centimeter the vessel is above or below the heart. For example, in a standing human, pressure in the veins of the feet is 90 mm Hg because of the distance from the heart to the feet. Conversely, veins above the heart tend to collapse, with the exception being veins inside the skull, where they are held open by surrounding bone. As a result, negative pressure can exist in the dural sinuses and air can be entrained immediately if these sinuses are entered during surgery.

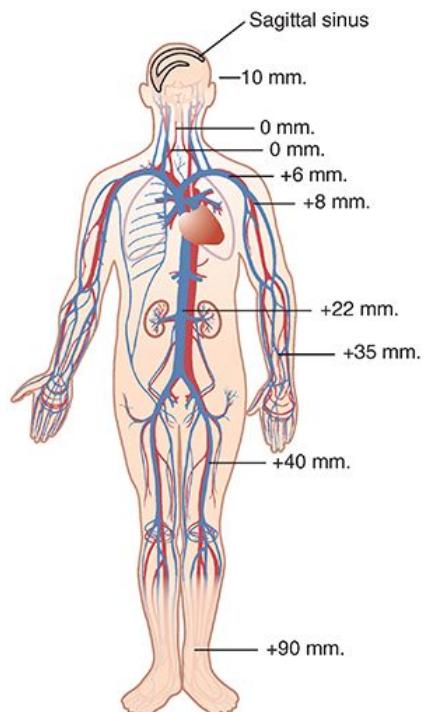


FIGURE 14.9 Effect of hydrostatic pressure on venous pressures throughout the body.

Hydrostatic pressure affects peripheral pressure in arteries and capillaries as well as veins. For example, a standing human who has a systemic blood pressure of 100 mm Hg at the level of the heart has a blood pressure of about 190 mm Hg in the feet.

Venous Valves and the Pump Mechanism

Valves in veins are arranged so that the direction of blood flow can be only toward the heart. In a standing human, movement of the legs compresses skeletal muscles and veins so blood is directed toward the heart. This venous pump or skeletal muscle pump is usually sufficient to maintain venous pressure below 25 mm Hg in a walking human. If an individual stands immobile, the venous pump does not function. As a result, pressures in the veins and capillaries of the legs can increase rapidly, resulting in leakage of fluid from the intravascular space. Indeed, as much as 15% of the blood volume can be lost from the intravascular space in the first 15 minutes of quiet standing.

Varicose Veins

Valves of the venous system can be destroyed when the veins are chronically distended by increased venous pressure as occurs during pregnancy or in an individual who stands most of the day. The end result is varicose veins characterized by bulbous protrusions of the veins beneath the skin of the legs. Venous and capillary pressures remain increased because of the incompetent venous pump, and this causes constant edema in the legs of these individuals. Edema interferes with diffusion of nutrients from the capillaries to tissues, so there is often skeletal muscle discomfort and the skin may ulcerate.

Blood Viscosity

Blood is a viscous fluid composed of cells and plasma. More than 99% of the cells in plasma are erythrocytes. As a result, leukocytes exert a minimal influence on the physical characteristics of blood. The percentage of blood comprising erythrocytes is the hematocrit, which to a large extent determines the viscosity of blood ([Figure 14.10](#)).⁴ When the hematocrit increases to 60% to 70%, viscosity of blood is increased about 10-fold compared with water, and flow through blood vessels is greatly decreased. Plasma protein concentrations influence blood viscosity only minimally.

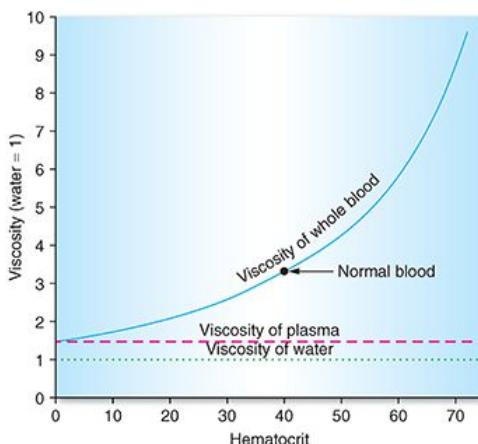


FIGURE 14.10 Hematocrit greatly influences the viscosity of blood. Reprinted from Guyton AC, Hall JE. Textbook of Medical Physiology. 10th ed. Philadelphia, PA: W.B. Saunders; 2000. Copyright © 2000 Elsevier. With permission.

Viscosity exerts fewer effects on blood flow in capillaries than in larger vessels. This most likely reflects alignment of erythrocytes as they pass through small blood vessels rather than the random arrangement characteristic of flow through larger vessels. This alignment of erythrocytes, which greatly decreases the viscous resistance that occurs normally between cells, is largely offset by a decreased velocity of flow that greatly increases viscosity. The net effect may be that viscous effects in small blood vessels are similar to those that occur in large blood vessels.

Plasma is considered extracellular fluid that is identical to interstitial fluid except for the greater concentrations of proteins (albumin, globulin, fibrinogen) in plasma. These greater concentrations reflect the inability of plasma proteins to pass easily through capillaries into the interstitial spaces. The presence of albumin creates colloid osmotic pressure, which prevents fluid from leaving the capillaries.

Determinants of Tissue Blood Flow

Tissue blood flow is directly proportional to the pressure difference between two points (not absolute pressure) and inversely proportional to resistance to flow through the vessel. This relationship between flow, pressure, and resistance can be expressed mathematically as a variant of Ohm's law, in which blood flow (amperes) is directly proportional to the pressure drop across two points (voltage) and inversely proportional to resistance ([Figure 14.11](#)). Rearrangement of this formula emphasizes that pressure is directly proportional to flow times resistance. Likewise, resistance is directly proportional to pressure and inversely proportional to flow. Furthermore, resistance is directly proportional to viscosity of blood and the length of the vessel and inversely proportional to the fourth power of the radius of the vessel (doubling the radius of the vessel or intravenous catheter size decreases resistance to flow 16-fold [Poiseuille law]).

$$\text{Blood Flow (Q)} = \frac{\text{Pressure Difference Between Two Points (P)}}{\text{Resistance to Flow (R)}}$$

$$\Delta P = Q \times R$$

$$R = \Delta P / Q$$

FIGURE 14.11 The relationship between blood flow, pressure, and resistance to flow can be expressed as a variant of Ohm's law.

It is important to understand that resistance to blood flow cannot be measured but rather is a calculated value based on measurement of driving pressures and the cardiac output. For example, systemic vascular resistance is calculated as the difference between mean arterial pressure and right atrial pressure divided by cardiac output. Pulmonary vascular resistance is calculated as the difference between mean pulmonary artery

pressure and left atrial pressure divided by the cardiac output. Resistance is expressed in dynes/s/cm⁻⁵ and is calculated by multiplying the equation for either systemic vascular resistance or pulmonary vascular resistance just described by a conversion factor of 80. If this factor of 80 is not applied, the simple equation of pressure difference divided by cardiac output results a resistance expressed as “wood units.” This is commonly used when describing pulmonary vascular resistance in the presence of pulmonary hypertension.

Conductance is the reciprocal of resistance and is a measure of the amount of blood flow that can pass through a blood vessel in a given time for a given pressure gradient.

Vascular Distensibility

Blood vessels are distensible such that increases in systemic blood pressure cause the vascular diameter to increase, which in turn decreases resistance to blood flow. Conversely, decreases in intravascular pressure increase the resistance to blood flow. The ability of blood vessels to distend as intravascular pressure increases varies greatly in different parts of the circulation. Anatomically, the walls of arteries are stronger than those of veins. As a result, veins are 6 to 10 times as distensible as arteries. Systemic blood pressure can eventually decrease to a level where intravascular pressure is no longer capable of keeping the vessel open. This pressure averages 20 mm Hg and is defined as the **critical closing pressure**. When the heart is abruptly stopped, the pressure in the entire circulatory system (mean circulatory pressure) equilibrates at about 7 mm Hg.

Vascular Compliance

Vascular compliance is defined as the increase in volume (capacitance) of a vessel produced by an increase in intravascular pressure. The compliance of the entire circulatory system is estimated to be 100 mL for each 1 mm Hg increase in intravascular pressure.⁴ The compliance of veins is much greater than that of arteries. For example, the volume of blood normally present in all veins is about 2,500 mL, whereas the arterial system contains only about 750 mL of blood when the mean arterial pressure is 100 mm Hg. Sympathetic nervous system activity can greatly alter the distribution of blood volume. Enhancement of sympathetic nervous outflow to the blood vessels, especially the veins, decreases the dimensions of the circulatory system, and the circulation continues to function almost normally even when as much as 25% of the total blood volume has been lost. **Vasoconstriction** or **vasodilation** refers to resistance changes in arterioles, whereas changes in the caliber of veins are described as **venoconstriction** or **venodilation**.

Control of Tissue Blood Flow

Control of blood flow to different tissues includes local mechanisms, autonomic nervous system responses, and release of hormones. Total tissue blood flow or cardiac output is about 5 L per minute, with large amounts being delivered to the heart, brain, liver, and kidneys (**Table 14.5**).⁴ In contrast, skeletal muscles represent 35% to 40% of body mass but receive only about 15% of the total cardiac output, reflecting the low metabolic rate of inactive skeletal muscles.

TABLE 14.5

Tissue blood flow^a

	Approximate blood flow (mL per minute)		Cardiac output (% of total)
	(mL/100 g per minute)		
Brain	750	50	15
Liver	1,450	100	29
Portal vein	1,100		
Hepatic artery	350		
Kidneys	1,000	320	20
Heart	225	75	5
Skeletal muscles (at rest)	750	4	15
Skin	400	3	8

Other tissues	425	2	8
Total	5,000		100

^aAdapted from Guyton AC, Hall JE. *Textbook of Medical Physiology*. 10th ed. Philadelphia, PA: W.B. Saunders; 2000. Copyright © 2000 Elsevier. With permission.

Local Control of Blood Flow

Local control of blood flow is most often based on the need for delivery of oxygen or other nutrients such as glucose or fatty acids to the tissues. The response to decreased oxygen delivery may reflect the local release of vasodilatory substances (adenosine, lactic acid, carbon dioxide, potassium ions), which results in increased tissue blood flow and oxygen delivery.

Autoregulation of Blood Flow

Autoregulation is a local mechanism that controls blood flow in which a specific tissue is able to maintain a relatively constant blood flow over a wide range of mean arterial pressures. When the mean arterial pressure increases, the associated increase in tissue blood flow causes the blood vessels to constrict, thereby limiting any increase in blood flow. Conversely, decreases in mean arterial pressure result in vasodilation, which maintains tissue blood flow. Autoregulatory responses to sudden changes in mean arterial pressure occur within 60 to 120 seconds. The ability of autoregulation to return local tissue blood flow to normal is incomplete.

Long-Term Control of Blood Flow

Long-term regulatory mechanisms that return local tissue blood flow to normal involve a change in vascularity of tissues. For example, sustained increases in mean arterial pressure to specific tissues, as occurs above a coarctation of the aorta, is accompanied by a decrease in the size and number of blood vessels. Likewise, if metabolism in a tissue becomes chronically increased, vascularity increases, or if metabolism is decreased, vascularity decreases. Indeed, inadequate delivery of oxygen to a tissue is the stimulus for the development of collateral vessels. Neonates exposed to increased concentrations of oxygen can manifest cessation of new vascular growth in the retina. Subsequent removal of the neonate from a high-oxygen environment causes an overgrowth of new vessels to offset the abrupt decrease in availability of oxygen. There may be so much overgrowth that the new vessels cause blindness (retrolental fibroplasia).

Autonomic Nervous System Control of Blood Flow

Autonomic nervous system control of blood flow is characterized by a rapid response time (within 1 second) and an ability to regulate blood flow to certain tissues at the expense of other tissues. The sympathetic nervous system is the most important component of the autonomic nervous system in the regulation of blood flow; sympathetic stimulation causes release of norepinephrine, which stimulates α -adrenergic receptors to produce vasoconstriction. Constriction of small arteries influences resistance to blood flow through tissues, whereas venoconstriction alters vascular capacitance and distribution of blood in the peripheral circulation. Sympathetic nervous system innervation is prominent in the kidneys and skin and minimal in the cerebral circulation.

Vasomotor Center

The vasomotor center, which is located in the pons and medulla, transmits sympathetic nervous system impulses through the spinal cord to all blood vessels. Evidence for a continuous, sustained state of partial vasoconstriction (vasomotor tone) is the abrupt decrease in systemic blood pressure that occurs when sympathetic nervous system innervation to the vasculature is abruptly interrupted, as by traumatic spinal cord transection or regional anesthesia. Activity of the vasomotor center can be influenced by impulses from a number of sites, including diffuse areas of the reticular activating system, hypothalamus, and cerebral cortex. Sympathetic nervous system impulses are transmitted to the adrenal medulla at the same time they are transmitted to the peripheral vasculature. These impulses stimulate the adrenal medulla to secrete epinephrine

and norepinephrine into the circulation, where they act directly on adrenergic receptors in the walls of vascular smooth muscle.

The medial and lower portions of the vasomotor center do not participate in transmission of vasoconstrictor impulses but rather function as an inhibitor of sympathetic nervous system activity, which allows blood vessels to dilate. Conceptually, this portion of the vasomotor center is functioning as the parasympathetic nervous system.

Mass Reflex

The mass reflex is characterized by stimulation of all portions of the vasomotor center, resulting in generalized vasoconstriction and an increase in cardiac output in an attempt to maintain tissue blood flow. The alarm reaction resembles the mass reflex, but associated skeletal muscle vasodilation and psychic excitement are intended to prepare the individual to confront a life-threatening situation.

Syncope

Emotional fainting (vasovagal syncope) may reflect profound skeletal muscle vasodilation such that systemic blood pressure decreases abruptly, and syncope occurs. Associated vagal stimulation results in bradycardia. This phenomenon may occur in patients who have an intense fear of needles, resulting in syncope during placement of an intravenous catheter.

Hormone Control of Blood Flow

Vasoconstrictor hormones that may influence local tissue blood flow include epinephrine, norepinephrine, angiotensin, and arginine vasopressin (formerly known as **antidiuretic hormone**). Bradykinin, serotonin, histamine, prostaglandins, and low circulating concentrations of epinephrine are vasodilating substances. Local chemical factors, such as accumulation of hydrogen ions, potassium ions, and carbon dioxide, relax systemic vascular smooth muscle and cause vasodilation.

Regulation of Systemic Blood Pressure

Systemic blood pressure is maintained over a narrow range by reciprocal changes in cardiac output and systemic vascular resistance. The autonomic nervous system and baroreceptors play a key role in moment-to-moment regulation of systemic blood pressure. Long-term regulation of blood pressure depends on control of fluid balance by the kidneys, adrenal cortex, and central nervous system.

Systolic, diastolic, and mean arterial pressure tends to increase progressively with age. Because a greater portion of the cardiac cycle is nearer the diastolic blood pressure, it follows that mean arterial pressure is not the arithmetic average of the systolic and diastolic blood pressures. Mean arterial blood pressure is the most important determinant of tissue blood flow because it is the average, tending to drive blood through the systemic circulation.

Rapid-Acting Mechanisms for the Regulation of Systemic Blood Pressure

Rapid-acting mechanisms for regulation of systemic blood pressure involve nervous system responses as reflected by the baroreceptor reflexes, chemoreceptor reflexes, atrial reflexes, and central nervous system ischemic reflex. These reflex mechanisms respond almost immediately to changes in systemic blood pressure. Furthermore, within about 30 minutes, these nervous system reflex responses are further supplemented by activation of hormonal mechanisms and shift of fluid into the circulation to readjust the blood volume. These short-term mechanisms can return systemic blood pressure toward but never entirely back to normal. Indeed, the impact of many of the rapid-acting regulatory mechanisms, such as the baroreceptor reflexes, diminishes with time as these mechanisms adapt to the new level of systemic blood pressure.

Baroreceptor Reflexes

Baroreceptors are nerve endings in the walls of large arteries in the neck and thorax, especially in the internal carotid arteries just above the carotid bifurcation and in the arch of the aorta ([Figure 14.12](#)).¹³ These nerve endings respond rapidly to changes in systemic blood pressure and are crucial for maintaining normal blood

pressure when an individual changes from the supine to standing position. An increase in mean arterial pressure produces stretch of baroreceptor nerve endings, and increased numbers of nerve impulses are transmitted to the depressor portion of the vasomotor center, leading to a relative decrease in the central nervous system outflow of sympathetic nervous system (vasoconstrictive) impulses ([Figure 14.13](#)).¹³ The net effects are vasodilation throughout the peripheral circulation, decreased heart rate, and decreased myocardial contractility, which all act to decrease systemic blood pressure back toward normal. Conversely, decreases in systemic blood pressure reflexively produce changes likely to increase blood pressure. Baroreceptors adapt in 1 to 3 days to sustained changes in systemic blood pressure, emphasizing that these reflexes are probably of no importance in long-term regulation of blood pressure. Volatile anesthetics, particularly halothane, inhibit the heart rate response portion of the baroreceptor reflex that occurs in response to changes in systemic blood pressure (see [Chapter 4](#)).

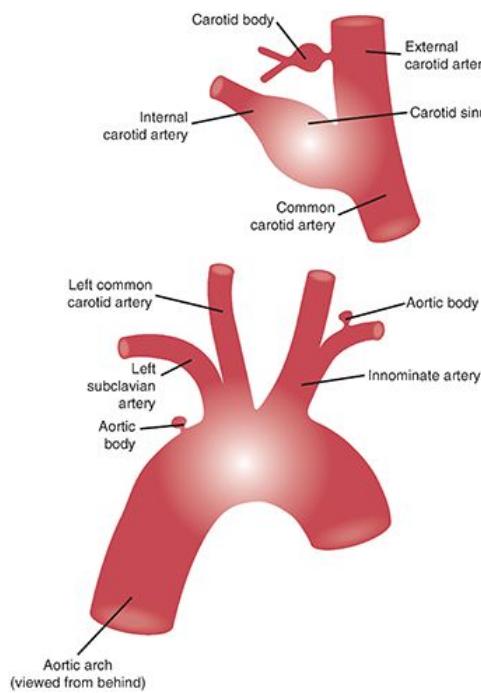


FIGURE 14.12 Baroreceptors are represented by the carotid sinus and receptors in the arch of the aorta. Chemoreceptors are located in the carotid and aortic bodies.

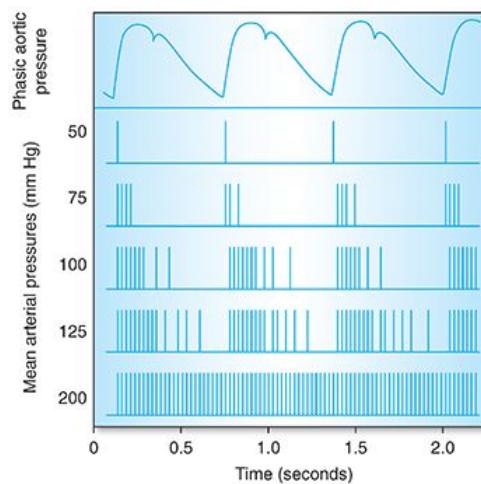


FIGURE 14.13 Discharges (vertical lines) in a single afferent nerve fiber from the carotid sinus at various arterial pressures plotted against changes in aortic pressure with time. Republished with permission of McGraw Hill LLC from Ganong WF. Review of Medical Physiology. 21st ed. New York, NY: Lange Medical Books/McGraw Hill, 2003; permission conveyed through Copyright Clearance Center, Inc.

Chemoreceptor Reflexes

Chemoreceptors are cells that transduce chemical signals into nerve impulses. There are chemoreceptors located in the carotid bodies and aortic body (see [Figure 14.12](#)).¹³ Each carotid or aortic body is supplied with an abundant blood flow through a nutrient artery so that the chemoreceptors are always exposed to oxygenated blood. When the systemic blood pressure, and thus the blood flow, decrease below a critical level, the chemoreceptors in the carotid body are stimulated by decreased availability of oxygen and also because of excess carbon dioxide and hydrogen ions that are not removed by the sluggish blood flow. Impulses from the chemoreceptors are transmitted to the vasomotor center, which results in reflex changes that tend to increase systemic blood pressure back toward the normal. Chemoreceptors do not respond strongly until systemic blood pressure decreases below 80 mm Hg. Chemoreceptors are more important in stimulating breathing when the PaO_2 decreases below 60 mm Hg (ventilatory response to arterial hypoxemia). The ventilatory response to arterial hypoxemia is inhibited by subanesthetic concentrations of most of the volatile anesthetics (0.1 minimum alveolar concentration) as well as injected drugs such as propofol, midazolam, barbiturates, and opioids (see [Chapters 4, 5, and 7](#)).

Bezold-Jarisch Reflex

The Bezold-Jarisch reflex is a circulatory response whereby a decrease in left ventricular volume activates receptors that cause a paradoxical bradycardia. This compensatory decrease in heart rate allows for increased ventricular filling but may also exacerbate hypotension. The bradycardia and hypotension that can occur during spinal or epidural anesthesia have been attributed to this reflex.

Atrial Reflexes

The atria contain low-pressure atrial stretch receptors similar to baroreceptors in large arteries. Stretching of the atria evokes reflex vasodilation and decreases the systemic blood pressure back toward the normal level. An increase in atrial pressure also causes an increase in heart rate (Bainbridge reflex) due to a direct effect of the increased atrial volume on stretch of baroreceptors located in both atria at the venoatrial junctions. The increase in heart rate evoked by stretching of the atria prevents accumulation of blood in the atria, veins, or pulmonary circulation.

Central Nervous System Ischemic Reflex

The central nervous system ischemic reflex response occurs when blood flow to the medullary vasomotor center is decreased to the extent that ischemia of this vital center occurs. As a result of this ischemia, there is an intense outpouring of sympathetic nervous system activity, resulting in profound increases in systemic blood pressure. It is believed that this reflex response is caused by failure of slowly flowing blood to remove carbon dioxide from the vasomotor center. The central nervous system reflex response does not become highly active until mean arterial pressure decreases to less than 50 mm Hg and reaches its greatest degree of stimulation at systemic blood pressures of 15 to 20 mm Hg. This reflex response is not useful for regulation of normal blood pressure but rather acts as an emergency control system to prevent further decreases in systemic blood pressure when cerebral blood flow is dangerously decreased.

Cushing Reflex

The Cushing reflex is a central nervous system ischemic reflex response that results from increased intracranial pressure. When intracranial pressure increases to equal arterial pressure, the Cushing reflex acts to increase systemic blood pressure above intracranial pressure. Cushing triad is defined as having (1)

hypertension, (2) bradycardia, and (3) irregular respirations (due to brainstem dysfunction). The latter is not often seen in this era, as most patients with severe intracranial hypertension are now mechanically ventilated.

Respiratory Variations in Systemic Blood Pressure

Systemic blood pressure normally varies by 4 to 6 mm Hg in a wavelike manner during quiet spontaneous breathing. Systemic blood pressure is increased during end-inspiration and the beginning of exhalation and decreased during the remainder of the breathing cycle. This is due to increased venous return to the right heart during inspiration, which takes a few cardiac cycles to be transmitted to the left heart. Positive pressure ventilation of the lungs produces a reversed sequence of blood pressure change because the initial positive airway pressure simultaneously pushes more blood toward the left ventricle causing an increase in pressure; this is followed by a decrease in left ventricular filling due to the decrease in venous return to the right heart caused by the positive intrathoracic pressure.

Continuous or beat-to-beat monitoring of the changes in arterial blood pressure, pulse pressure, and stroke volume occurring during mechanical ventilation may provide an indication of the patient's ability to respond to volume administration with an increase in cardiac output or "fluid responsiveness." Respiratory variation in these parameters of more than 12% to 15% generally indicates fluid responsiveness. When the chest is closed and an adequate tidal volume is employed, "goal-directed" fluid resuscitation can be guided by such measurements.

Heart Rate Variability

Variations in heart rate occur during normal respiration, whereby inspiration increases heart rate and expiration decreases it. High-frequency heart rate variability is controlled by autonomic reflexes mediated by neural input to the heart supplied by the vagus nerve. Low-frequency heart rate variability results from the interaction between parasympathetic and sympathetic tone. Analysis of heart rate variability provides information regarding the integrity of the autonomic nervous system. High heart rate variability is a sign of good health, and conversely, low heart rate variability can be a manifestation of disease (myocardial infarction, heart failure, neuropathy) and occurs universally following the denervation that occurs during cardiac transplantation.¹⁴

Systemic Blood Pressure Vasomotor Waves

Cyclic increases and decreases in systemic blood pressure lasting 7 to 10 seconds are referred to as **vasomotor** or **Traube-Hering waves**. The presumed cause of vasomotor waves is oscillation in the reflex activity of baroreceptors. For example, increased systemic blood pressure stimulates baroreceptors, which then inhibit the sympathetic nervous system, causing a decrease in systemic blood pressure. Decreased systemic blood pressure decreases baroreceptor activity and allows the vasomotor center to become active once again, increasing the systemic blood pressure to a higher value.

Moderately Rapid-Acting Mechanisms for the Regulation of Systemic Blood Pressure

There are at least three hormonal mechanisms that provide either rapid or moderately rapid control of systemic blood pressure. These hormonal mechanisms are catecholamine-induced vasoconstriction, renin-angiotensin-induced vasoconstriction, and vasoconstriction induced by arginine vasopressin, all of which increase systemic blood pressure by increasing systemic vascular resistance. Circulating catecholamines may even reach parts of the circulation that are devoid of sympathetic nervous system innervation, such as metarterioles. Renin-angiotensin-induced vasoconstriction manifests to a greater degree on arterioles than veins and requires about 20 minutes to become fully active.

In addition to hormonal mechanisms, there are two intrinsic mechanisms (capillary fluid shift and stress-relaxation of blood vessels), which begin to react within minutes of changes in systemic blood pressure. For example, changes in systemic blood pressure produce corresponding changes in capillary pressure, thus allowing fluid to enter or leave the capillaries to maintain a constant blood volume. Stress relaxation is the gradual change in blood vessel size to adapt to changes in systemic blood pressure and the amount of blood

that is available. The stress-relaxation mechanism has definite limitations such that increases in blood volume greater than about 30% or decreases of more than about 15% cannot be corrected by this mechanism alone.

Long-Term Mechanisms for the Regulation of Systemic Blood Pressure

Long-term mechanisms for the regulation of systemic blood pressure, unlike the short-term regulatory mechanisms, have a delayed onset but do not adapt, providing a sustained regulatory effect on systemic blood pressure. The renal–body fluid system plays a predominant role in long-term control of systemic blood pressure because it controls both the cardiac output and systemic vascular resistance. This crucial role is supplemented by accessory mechanisms, including the renin-angiotensin-aldosterone system and arginine vasopressin regulation.

Renal–Body Fluid System

Increased systemic blood pressure, as provoked by modest increases in blood volume, results in sodium ion and water excretion by the kidneys. The resultant decrease in blood volume leads to decreases in cardiac output and systemic blood pressure. After several weeks, the cardiac output returns toward normal, and systemic vascular resistance decreases to maintain the lower but more acceptable blood pressure. Conversely, a decrease in systemic blood pressure stimulates the kidneys to retain fluid. A special feature of this regulatory mechanism is its ability to return systemic blood pressure completely back to normal values. This contrasts with rapid-acting to moderately rapid-acting mechanisms, which cannot return systemic blood pressure entirely back to normal.

Renin-Angiotensin System

Aldosterone secretion that results from the action of angiotensin II on the adrenal cortex exerts a long-term effect on systemic blood pressure by stimulating the kidneys to retain sodium and water. The resulting increase in extracellular fluid volume causes cardiac output, and subsequently systemic blood pressure, to increase.

Regulation of Cardiac Output and Venous Return

Cardiac output is the amount of blood pumped by the left ventricle into the aorta each minute (product of stroke volume and heart rate), and venous return is the amount of blood flowing from the veins into the right atrium each minute. Because the circulation is a closed circuit, the cardiac output must equal venous return. Cardiac output for the average person weighing 70 kg and with a body surface area of 1.7 m^2 is about 5 L per minute. This value is about 10% less in women.

Determinants of Cardiac Output

Venous return is the main determinant of cardiac output. The metabolic requirements of tissues control cardiac output through alterations in resistance to tissue blood flow. For example, increased local metabolic needs lead to regional vasodilation, with a resulting increase in tissue blood flow and thus venous return. Cardiac output is increased by an amount equivalent to the venous return.

Any factor that interferes with venous return can lead to decreased cardiac output. Hemorrhage decreases blood volume such that venous return decreases and cardiac output decreases. Acute venodilation, such as that produced by spinal anesthesia and accompanying sympathetic nervous system blockade, can so increase the capacitance of peripheral vessels that venous return is reduced and cardiac output declines. Restoration of venous tone (with a vasoconstrictor) and/or administration of fluid can restore cardiac output. Positive pressure ventilation of the lungs, particularly in the presence of a decreased blood volume, causes a decrease in venous return and cardiac output.

Factors that increase cardiac output are associated with decreases in systemic vascular resistance. For example, anemia decreases the viscosity of blood, leading to a decrease in systemic vascular resistance and increase in venous return. An increased blood volume increases cardiac output by increasing the gradient for flow to the right atrium and by distending blood vessels, which decreases resistance to blood flow. Increased cardiac output caused by an increased blood volume lasts only 20 to 40 minutes because increased capillary

pressures cause intravascular fluid to enter tissues, thereby returning blood volume to normal. Furthermore, increased pressure in veins caused by the increased blood volume causes the veins to distend (stress relaxation). Cardiac output increases during exercise, in hyperthyroidism, and in the presence of arteriovenous shunts associated with hemodialysis, reflecting decreases in systemic vascular resistance.

Sympathetic nervous system stimulation increases myocardial contractility and heart rate to increase cardiac output beyond that possible from venous return alone. Maximal stimulation by the sympathetic nervous system can double cardiac output. Nevertheless, this sympathetic nervous system–induced increase of cardiac output is only transient, despite sustained increases in nervous system activity. A reason for this transient effect is autoregulation of tissue blood flow, which manifests as vasoconstriction to decrease venous return and thus decrease cardiac output back toward normal. In addition, increased systemic blood pressure associated with increases in the cardiac output causes fluid to leave the capillaries, thereby decreasing blood volume, venous return, and cardiac output.

An increase in myocardial contractility or inotropy can increase the stroke volume and thereby the cardiac output. Cardiac muscle is sensitive to calcium; most hormones and drugs that increase contractility augment intracellular calcium use. One newer agent available outside of the United States that is used to provide inotropic support in severe heart failure (levosimendan) sensitizes the myofibrils to calcium. Decreased contractility is caused by many anesthetic agents. Strictly speaking, changes in inotropic state should be defined in the absence of changes in preload and afterload; because many inotropic drugs affect these parameters as well, changes in cardiac output are not always due only to the inotropic activity.

Ventricular Function Curves

Ventricular function curves (Frank-Starling curves) depict the cardiac output at different atrial (ventricular end diastolic) filling pressures ([Figure 14.14](#)). Clinically, ventricular function curves are used to estimate myocardial contractility. Improved cardiac function (sympathetic nervous system stimulation) is characterized by a shift of the cardiac output curve to the left of the normal curve (greater cardiac output for a given filling pressure), whereas a shift of the curve to the right of normal (myocardial infarction, cardiomyopathy) reflects decreased cardiac function. Even with a normal ventricular function curve, as preload is increased, a point is reached where further stretching of the cardiac muscle results in no further increase and eventually to a decrease in cardiac output.

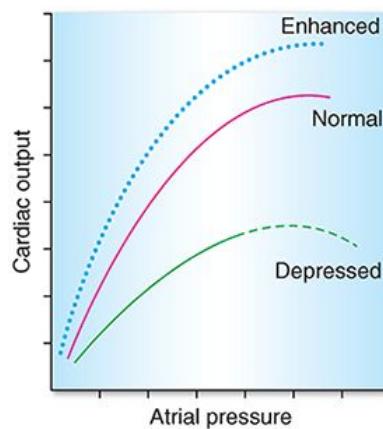


FIGURE 14.14 Ventricular function curves (Frank-Starling curves) depict the volume of forward ventricular ejection (cardiac output) at different atrial filling pressures and varying degrees of myocardial contractility.

Pressure-Volume Loops

Pressure-volume loops describe the dynamic characteristics of cardiac function ([Figure 14.15](#)). If ventricular pressure is plotted against ventricular volume, each cardiac cycle can be depicted by a pressure-volume loop.

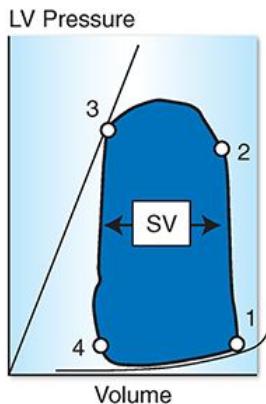


FIGURE 14.15 Pressure-volume loop representing one cardiac cycle for the left ventricle. The four segments of the loop represent, respectively: diastole or ventricular filling ending in mitral valve closure (point 1), isovolumic contraction ending in aortic valve opening (point 2), systole ending in aortic valve closure (point 3), and isovolumic relaxation ending in mitral valve opening (point 4). The width of the loop is the stroke volume; the end-systolic relationship (line through point 3) is a measure of contractility with increased contractility reflected by a steeper slope, and decreased contractility with a shallower slope.

Shock Syndromes

Circulatory shock is characterized by inadequate tissue blood flow and oxygen delivery to cells resulting in generalized deterioration of cellular and organ function. Inadequate tissue flow is due to inadequate cardiac output and can result from decreased venous return, myocardial depression, or both. Cellular metabolism is depressed, and the amount of heat liberated is decreased resulting in a decreased body temperature particularly when the ambient environment is cold. In the early stages of shock, consciousness is usually maintained, although mental clarity may be impaired. Consciousness is likely to be lost as shock progresses. Low cardiac output greatly decreases urine output, eventually leading to anuria as glomerular pressure decreases below the critical value required for filtration of fluid into Bowman's capsule. Furthermore, the kidneys have such a high rate of metabolism that decreased renal blood flow may cause acute tubular necrosis (see [Chapter 16](#)). An important feature of persistent shock is eventual progressive deterioration of the heart. In addition to myocardial depression caused by decreased coronary artery blood flow, myocardial function can also be depressed by lactic acid, bacterial endotoxins, and myocardial depressant factor released from an ischemic pancreas.

Hemorrhagic Shock

Hemorrhage is the most common cause of shock due to decreased venous return. Any decrease in systemic blood pressure initiates powerful baroreceptor-mediated increases in sympathetic nervous system activity, manifesting as arterial constriction, vasoconstriction, and direct myocardial stimulation. Vasoconstriction is particularly important for sustaining venous return to the heart and, thus, maintaining cardiac output. Arterial constriction is responsible for initially maintaining systemic blood pressure despite decreases in cardiac output. This maintenance of systemic blood pressure sustains cerebral and coronary artery blood flow as significant vasoconstriction does not occur in these organs. In other organs, such as the kidneys, intense sympathetic nervous system-mediated vasoconstriction may decrease blood flow dramatically.

Nonhemorrhagic Hypovolemic Shock

Loss of plasma volume from the circulation can result in shock similar to that produced by hemorrhage. Intestinal obstruction results in fluid loss into the gastrointestinal tract and reduction in plasma volume. Severe burns may also be associated with sufficient loss of plasma volume to result in shock. Severe dehydration from any cause can also lead to hypovolemic shock due to reduction in plasma volume. Hypovolemic shock that results from a reduction in plasma volume has the same clinical characteristics as

hemorrhagic shock except that selective reduction of the plasma volume greatly increases the viscosity of blood and exacerbates sluggish blood flow.

Neurogenic Shock

Neurogenic shock occurs in the absence of blood loss when vascular capacity increases so greatly that even a normal blood volume is not capable of maintaining venous return and cardiac output. Common causes of loss of vasomotor tone and subsequent neurogenic shock are traumatic transection of the spinal cord and acute blockade of the peripheral sympathetic nervous system by spinal or epidural anesthesia.

Septic Shock

Septic shock is characterized by profound peripheral vasodilation, increased cardiac output secondary to decreased systemic vascular resistance, increased vascular permeability with fluid loss from the vascular compartment, and development of disseminated intravascular coagulation. Septic shock is most commonly caused by gram-positive bacteria and less commonly by endotoxin-producing gram-negative bacteria. Endotoxins are bacterial membrane lipopolysaccharides that are made up of a toxic fatty acid (lipid A) core and a complex polysaccharide coat. Analogous molecules in the walls of gram-positive bacteria and fungi can also cause septic shock. The septic response is likely to reflect a systemic inflammatory response produced by exposure to bacterial cell products that ultimately lead to a progressively dysfunctional host response and multisystem organ failure. Elderly patients and those with immunosuppression are vulnerable to the development of sepsis and associated septic shock. The end stages of septic shock are not greatly different from the end stages of hemorrhagic shock, even though the initiating factors are markedly different. Mortality approaches 50% in septic shock despite significant improvements in supportive care.¹⁵

Measurement of Cardiac Output

The management of patients in the operating room and intensive care unit involves therapeutic interventions intended to optimize tissue oxygen delivery. Common interventions include fluid administration, blood transfusion, inotrope and vasoactive pharmacotherapy, heart rate and rhythm manipulation, mechanical assist devices, and mechanical ventilation. Ideally these therapies should be guided by measures of adequacy of tissue oxygenation or perfusion, but such measures are not yet clinically available. Indicators of global adequacy of perfusion such as serum lactate or central venous oxygen saturation are helpful, but abnormal values may take time to develop making the clinical response reactive rather than proactive. Cardiac output can be measured clinically by a variety of techniques and can be used to guide therapy.

Traditionally, cardiac output measurement has required insertion of a thermistor-tipped pulmonary artery catheter. Recent advances in microprocessor technology, a greater awareness of the limitations and hazards of pulmonary artery catheter insertion, and a need to measure cardiac output in out of operating room settings such as the emergency department, have led to the development of newer monitoring techniques. The general trend has been to develop techniques that are less invasive and allow more frequent, or even continuous, measurement of cardiac output.¹⁶ Nevertheless, the pulmonary artery thermodilution technique represents the clinical standard against which new techniques are compared.¹⁷ Currently used methods of cardiac output measurement include Fick methods, indicator dilution methods, thermodilution, echocardiographic techniques, impedance cardiography, and pulse contour analysis.

Fick Method

Adolf Fick first described use of the “Fick principle” to estimate cardiac output in 1870. Cardiac output is estimated by dividing the oxygen consumption by the arteriovenous difference for oxygen ([Figure 14.16](#)).⁴ Oxygen consumption is measured by a respirometer containing a known oxygen mixture. The patient’s exhaled gases are collected in a large inflatable reservoir (Douglas bag). The volume and oxygen concentrations of the exhaled gases are measured, allowing calculation of oxygen consumption. Clinically, this is rarely feasible, and a nomogram is used to estimate oxygen consumption.

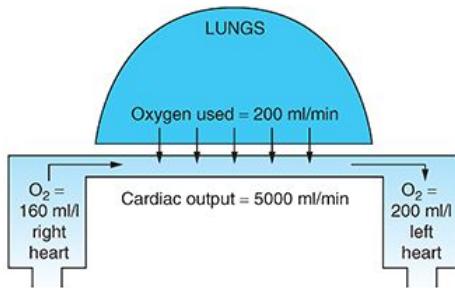


FIGURE 14.16 The Fick method calculates cardiac output as oxygen consumption divided by the arteriovenous difference for oxygen. Republished with permission of McGraw Hill LLC from Ganong WF. Review of Medical Physiology. 21st ed. New York, NY: Lange Medical Books/McGraw Hill, 2003; permission conveyed through Copyright Clearance Center, Inc.

Venous blood used for calculation of oxygen content must be obtained from the right ventricle, or, ideally, the pulmonary artery, to ensure adequate mixing. Blood from the right atrium may not yet be adequately mixed to provide a true mixed venous sample. Blood used for determining the oxygen saturation in arterial blood can be obtained from any artery because all arterial blood is thoroughly mixed before it leaves the heart and therefore has the same concentration of oxygen. With the assumption of oxygen consumption from a nomogram, and the need for a mixed venous sample that requires a pulmonary artery catheter, the Fick technique has largely been supplanted by thermodilution, where all the variables in the equation are measured (see “[Indicator Dilution Method](#)” and “[Thermodilution Method](#)” below).

Indicator Dilution Method

In measuring the cardiac output by the indicator dilution method, a nondiffusible dye (indocyanine green) is injected into the right atrium (or central venous circulation), and the concentration of dye is subsequently measured continuously in the arterial circulation by a spectrophotometer. The area under the resulting time-concentration curve before recirculation of the dye occurs, combined with knowing the amount of dye injected, allows calculation of the pulmonary blood flow, which is the same as the cardiac output. It is necessary to extrapolate the dye curve to zero because recirculation of the dye occurs before the down slope of the curve reaches baseline. Early recirculation of the dye may indicate the presence of a right-to-left intracardiac shunt (foramen ovale), permitting direct passage of a portion of the dye to the left side of the heart without first passing through the lungs.

Thermodilution Method

A bolus of cold fluid may also be considered an indicator and used in the indicator dilution technique. A pulmonary artery catheter with ports in the right atrium and pulmonary artery and a temperature sensor on the distal port is used to measure thermodilution cardiac outputs. Thermodilution cardiac outputs are determined by measuring the change in blood temperature between two points (right atrium and pulmonary artery) after injection of a known volume of cold saline solution at the proximal right atrial port. The change in blood temperature as measured at the distal pulmonary artery port is inversely proportional to pulmonary blood flow (the extent to which the cold saline solution is diluted by blood), which is equivalent to cardiac output. The area under the temperature-time curve is converted to its equivalent in cardiac output. The main assumptions with this technique are unidirectional flow (no right sided valvular regurgitation) and no intracardiac shunts. Advantages of this technique compared with the dye dilution method include dissipation of cold in tissues so recirculation is not a problem, and safety of repeated and frequent measurements because saline is innocuous unless very frequent measurements incur a significant volume load. A modification of this technique is the use of a heated filament around the pulmonary artery catheter to create a small heat signal, and a high sensitivity thermistor to sense the signal. Using sophisticated signal processing, and a sequence of heat application that is repeated every 30 seconds, a semicontinuous automated cardiac output measurement is obtained.

Echocardiographic Techniques

Echocardiography can be used to estimate cardiac output by combining the Doppler principle to determine the velocity of blood in the aorta with two-dimensional views to determine aortic diameter.¹⁶ Conventional transesophageal or transthoracic echocardiographic techniques have the advantage that systolic and diastolic function, volume status, regional wall abnormalities, valve function, and the presence of pericardial effusion may also be evaluated. However, this technique requires significant operator expertise. More recently, Doppler techniques have been developed using transesophageal probes designed solely for the purpose of estimating cardiac output. Aortic dimensions are not measured but are estimated from age-, sex-, and body size-specific nomograms derived from large population studies. Transesophageal Doppler estimates of cardiac output require minimal operator training and allow rapid cardiac output estimation.

Impedance Cardiography

The thorax is a conductor whose impedance is altered by changes in blood volume and velocity with each cardiac cycle. Impedance cardiography is based on the principle of thoracic electrical bioimpedance and involves the placement of electrodes to allow the transmission of current and measurement of voltage across the chest.¹⁸ Thus, thoracic electrical bioimpedance techniques can be used to noninvasively estimate cardiac output. However, the reliability of this technique is limited under several circumstances including patient movement, poor electrocardiogram signal quality, cardiac tachydysrhythmias, excessive thoracic fluid, and open chest wounds with metal retractors.

Pulse Contour Analysis

The first attempt to determine cardiac output from analysis of the pulse contour was made in 1904. The aortic pressure waveform is a function of the stroke volume and its interaction with the vascular tree. The arterial pulse contour can be modeled in a manner analogous to an electrical circuit that has specific values for resistance, compliance, and impedance.¹⁹ Thus, the flow within that system can be estimated from the pressure waveform that is generated. There are several devices now available, using different methods of analysis, which estimate the stroke volume and cardiac output from analysis of the arterial waveform (from an arterial catheter).²⁰ An enhancement of this technique is estimating “stroke volume variation” with respiration in mechanically ventilated patients. As referred to the discussion earlier, a variation of more than 12% to 15% indicates the patient will likely increase their cardiac output if fluid is administered.

Microcirculation

The circulation exists to supply tissues with blood in amounts commensurate with their needs for oxygen and nutrients.⁴ The microcirculation is defined as the circulation of blood through the smallest vessels of the body—arterioles, capillaries, and venules. Capillaries, whose walls consist of a single layer of endothelial cells, serve as the site for the rapid transfer of oxygen and nutrients to tissues and receipt of metabolic byproducts. There are an estimated 10 billion capillaries providing a total surface area that exceeds 6,300 m² for nutrient exchange. Capillary density varies from tissue to tissue. Capillaries are numerous in metabolically active tissues, such as cardiac and skeletal muscles, whereas in less active tissues, capillary density is low. Nevertheless, it is unlikely that any functional cell is greater than 50 microns away from a capillary. The muscular arterioles serve as the major resistance vessels and regulate regional blood flow to the capillary beds. Venules act primarily as collecting channels and storage vessels.

Anatomy of the Microcirculation

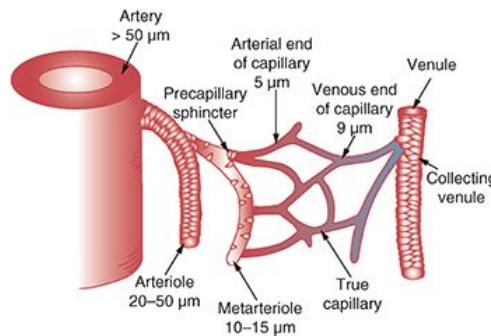
Arterioles give rise to metarterioles, which give rise to capillaries (**Table 14.6**; **Figure 14.17**).¹³ Other metarterioles serve as thoroughfare channels to the venules, bypassing the capillary bed. Capillaries drain via short collecting venules to the venules. Blood flow through capillaries is regulated by muscular precapillary sphincters present at the capillary opening. The arterioles, metarterioles, and venules contain smooth muscle. As a result, the arterioles serve as the major resistance vessels and regulate regional blood flow to the capillary beds, whereas the venules and veins serve primarily as collecting channels and storage or capacitance vessels.

TABLE 14.6

Anatomy of the various types of blood vessels

Vessel	Lumen diameter	Approximate cross-sectional area (cm ²)	Percentage of blood volume contained
Aorta	2.5 cm	2.5	
Artery	0.4 cm	20	13
Arteriole	30 microns	40	1
Capillary	5 microns	2,500	6
Venule	20 microns	250	
Vein	0.5 cm	80	64 ^a
Vena cava	3 cm	8	
Heart			7
Pulmonary circulation		18	9

^aBlood volume contained in venules, veins, and vena cava.

**FIGURE 14.17** Anatomy of the microcirculation.

Capillary walls are about 1 micron thick, lined on the endovascular surface with the glycocalyx ([Figure 14.18](#)). Channels through the endothelium include fenestrations or pores²¹ and interdigitated junctions between cells. The tissue side of the endothelial cell is lined with a basement membrane in many tissues. The structure of the capillary wall varies from tissue to tissue, but in many organs, including those in skeletal, cardiac, and smooth muscle, the interdigitated junction between endothelial cells allows passage of molecules up to 10 nm in diameter. In addition, the cytoplasm of endothelial cells is attenuated to form gaps or pores that are 20 to 100 nm in diameter. These pores permit the passage of relatively large molecules. It also appears that plasma and its dissolved proteins are taken up by endocytosis, transported across endothelial cells, and discharged by exocytosis into the interstitial fluid. In the brain, the capillaries resemble those in skeletal muscles, except the interdigitated junctions between endothelial cells are tighter (blood–brain barrier), permitting passage of only small molecules.

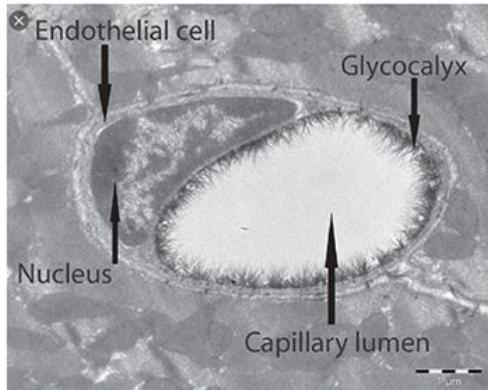


FIGURE 14.18 Transmission electron microscopic image of the glycocalyx in a left ventricular myocardial capillary following Alcian blue 8GX staining. The capillary lumen is enclosed by the endothelial cell. The luminal side of the endothelium is aligned by a polysaccharide layer containing proteoglycans (PG) and glycoproteins (GP). This is the static, membrane-bound part of the glycocalyx. The dynamic part, containing the plasma constituents, is not visualized due to collapse following the preparation and staining procedures. *From Haeren RHL, van de Ven SEM, van Zandvoort MAMAJ, et al. Assessment and imaging of the cerebrovascular glycocalyx. Curr Neurovasc Res. 2016;13(3):249-260.*

The diameter of capillary pores is about 25 times the diameter of water molecules (0.3 nm), which are the smallest molecules that normally pass through capillary channels. Plasma proteins have diameters that exceed the width of capillary pores. Other substances, such as sodium, potassium, and chloride ions and glucose, have intermediate diameters (0.39–0.86 nm) such that permeability of capillary pores for different substances varies according to their molecular weights ([Table 14.7](#)). Oxygen and carbon dioxide are both lipid soluble and readily pass through endothelial cells.

TABLE 14.7

Permeability of capillary membranes

	Molecular weight (da)	Relative permeability
Water	18	1.0
Sodium chloride	58.5	0.96
Glucose	180	0.6
Hemoglobin	66,700	0.01
Albumin	69,000	0.0001

True capillaries are devoid of smooth muscle and are therefore incapable of active constriction. Nevertheless, the endothelial cells that form them contain actin and myosin and can alter their shape in response to certain chemical stimuli. The diameter of capillaries (7–9 µm) is just sufficient to permit erythrocytes to squeeze through in single file. The thin walls of capillaries are able to withstand high intraluminal pressures because their small diameter prevents excessive wall tension (Laplace law).

Blood Flow in Capillaries

Blood flow in capillaries is approximately 1 mm per second and is intermittent rather than continuous. This intermittent blood flow reflects contraction and relaxation of metarterioles and precapillary sphincters in alternating cycles 6 to 12 times per minute.²² The phenomenon of alternating contraction and relaxation is known as **vasomotion**. Oxygen is the most important determinant of the degree of opening and closing of metarterioles and precapillary sphincters. A low P_{O_2} allows more blood to flow through capillaries to supply tissues. In this regard, the impact of oxygen on capillary blood flow provides a form of autoregulation of tissue blood flow.

In addition to nutritive blood flow through tissues that is regulated by oxygen, there is also nonnutritive (shunt) blood flow regulated by the autonomic nervous system. The nonnutritive blood flow is characterized by direct vascular connections between arterioles and venules. Some of these arteriovenous connections have muscular coverings so blood flow can be altered over a wide range. In some parts of the skin, these arteriovenous anastomoses provide a mechanism to permit rapid inflow of arterial blood to warm the skin and dissipate the heat.

Vasoactive Role of the Capillary Endothelium

True capillaries are devoid of smooth muscle and are therefore incapable of active constriction. Nevertheless, the endothelial cells that form them contain actin and myosin and can alter their shape in response to certain chemical and mechanical stimuli. The diameter of capillaries (7-9 μm) is just sufficient to permit erythrocytes to squeeze through in single file. The thin walls of capillaries are able to withstand high intraluminal pressures because their small diameter prevents excessive wall tension (Laplace law).

Prostacyclin, produced by the endothelium, can relax vascular smooth muscle via an increase in cyclic adenosine monophosphate concentration. Prostacyclin is formed in the endothelium from arachidonic acid, and the reaction is catalyzed by prostacyclin synthase. The principal function of prostacyclin is to inhibit platelet adherence to the endothelium and platelet aggregation and thus prevent intravascular clot formation.

The formation and release of NO is also important in the endothelium-mediated vascular dilation.²³ The NO is released when endothelial cells are stimulated by acetylcholine or other vasodilator substances (adenosine triphosphate, bradykinin, serotonin, substance P, and histamine). The NO release can be stimulated by the shear stress of blood flow on the endothelium. A vasoconstrictor peptide synthesized by the capillary endothelium is endothelin. Endothelin may affect vascular tone and blood pressure.

Fluid Movement Between the Capillary Lumen and the Interstitium

Glycocalyx

The understanding of factors determining fluid movement between the capillary lumen and the interstitial space has been revolutionized in the last 25 years by identification and study of the glycocalyx.^{24,25} This is a complex hydrated gel-like layer of proteoglycans and glycoproteins anchored to the endothelium and forming an extensive matrix in which there are also soluble proteins; the glycocalyx interacts with plasma proteins, principally albumin, to form a thicker layer sometimes termed the *endothelial surface layer*. The mean thickness of the glycocalyx in man appears to be approximately 0.5 microns,²⁶ varying by size of vessel and tissue. Remarkably, it has been estimated the total body volume of the glycocalyx approaches 1.7 L.²⁷ The properties of the glycocalyx and the subglycocalyx immediately adjacent to the endothelial cell surface and in the junctions between cells are major determinants of vascular permeability and fluid movement.

Prior to the identification of the glycocalyx, fluid movement to and from the vascular and interstitial compartments was thought to follow the “Starling equation”²⁸ where the hydrostatic and oncotic pressures in the capillary lumen and interstitium, and the cell wall permeability, largely at the site of cell junctions and transmembrane fenestrations or pores, to solutes and proteins (see **Table 14.7**) were principal determinants of fluid flow. In this model at the proximal (arterial) end of the capillary, the net force was to drive protein-free fluid into the interstitium, and at the distal (venous) end of the capillary, the net force was for fluid reabsorption back into the vascular space. Higher hydrostatic pressure in the proximal capillary and higher oncotic pressure in the distal capillary were presumed to be the predominating forces.

In the hundred years following these original concepts, it has become apparent there are significant differences between tissues in the movement of fluid, electrolytes, and proteins across capillary walls. Perhaps most important is experimental studies which failed to demonstrate significant fluid reabsorption at the venous end of the capillary beds of most tissues and showed instead that lymphatic drainage (see following text) is the principal mechanism of maintaining interstitial fluid volume. Rather than the oncotic forces of fluid flux being across the endothelium and its intercellular junctions and pores, it is now apparent that the transglycocalyx oncotic forces determine fluid flux and the glycocalyx is the “molecular sieve” for proteins, predominantly albumin which is largely bound within the glycocalyx, leading to a low subglycocalyx oncotic pressure. This prevents significant fluid reabsorption at the distal capillary. Disruptions

in the glycocalyx result in large increases in capillary hydraulic permeability and protein flux, confirming its important role in this regard. Thus, the original concept of Starling has been revised to the “modified” Starling equation recognizing the transglycocalyx rather than transendothelial forces, with a major contribution from the low oncotic pressure in the subglycocalyx.

In addition to its role in regulating fluid flux, the glycocalyx appears to have, through its complex proteoglycan structure, mechanosensory properties that can translate shear stress and blood pressure elevation to the endothelial cells, inducing nitric oxide production and vasodilation. It also affects local blood viscosity and hematocrit to enhance flow, preventing red cells from contact with the endothelium and preventing interaction of inflammatory cells and platelets with the endothelial cell surface.

The Glycocalyx in Disease States

Damage or loss of the glycocalyx could be predicted to result in tissue edema and inflammation. [Figure 14.19](#) illustrates the normal glycocalyx (left side of illustration) and how loss of the glycocalyx in sepsis (mid and right side of illustration) leads to exposure of adhesion molecules on the endothelial cell surface promoting adhesion of leukocytes, platelets, and then thrombus formation as well as capillary fluid leakage and edema formation.²⁹

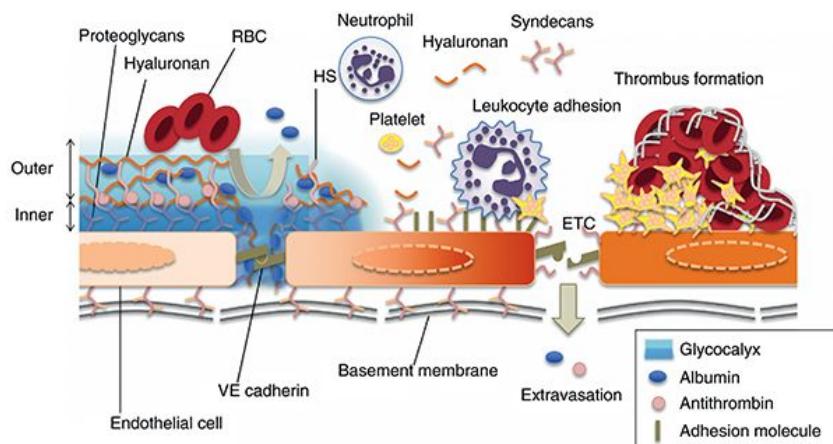


FIGURE 14.19 Derangement of the endothelial glycocalyx in sepsis. From Iba T, Levy JH. Derangement of the endothelial glycocalyx in sepsis. *J Thromb Haemostasis*. 2019;17(2):283-294.

Other disease states associated with glycocalyx shedding or injury include acute hypervolemia, through atrial natriuretic peptide production (due to atrial distension), hemorrhage, ischemia-reperfusion injury, and hyperglycemia.

Detection of glycocalyx damage or loss and therapy to minimize or treat such loss remains experimental, but hypervolemia and hyperglycemia which can be prevented by the anesthesiologist appear likely to be protective. Study of the glycocalyx also contributes to arguments regarding the types of fluid recommended for resuscitation in different settings.³⁰

Diffusion

Oxygen and carbon dioxide (and anesthetic gases) are lipid soluble and transfer directly across cell membranes independent of pores and independent of the function of the glycocalyx. The diffusion rate of these gases is directly proportional to the concentration difference between the two sides of the membrane. For this reason, oxygen moves from the capillaries into the tissues while carbon dioxide moves in the opposite direction. Typically, only slight partial pressure differences suffice to maintain adequate transport of oxygen from the plasma into the cells and interstitium.

Lymphatics

Lymphatic drainage represents the major route by which fluid flows from the interstitial spaces back into the bloodstream. In the steady state, there is continuous flow from one compartment to the next. While the lymphatic vessels drain into major veins in the neck, approximately half the total flow is absorbed by microvessels in the lymph nodes, leading to a total flow of approximately 8 L per day, meaning the entire plasma volume (not including proteins) leaves the circulation every 9 hours.²⁵

Anatomy

The major terminal lymph vessels are the thoracic duct and the right lymphatic duct ([Figure 14.20](#)). The thoracic duct is the larger of the two (2 mm in diameter), entering the venous system in the angle of the junction of the left internal jugular and subclavian veins. The right lymphatic duct is not always present, and if it is, it rarely exists as such because the three vessels that occasionally unite to form it usually open separately into the right internal jugular, subclavian, and innominate veins. Damage (surgical or traumatic) to a thoracic duct can cause intrathoracic fluid accumulation.

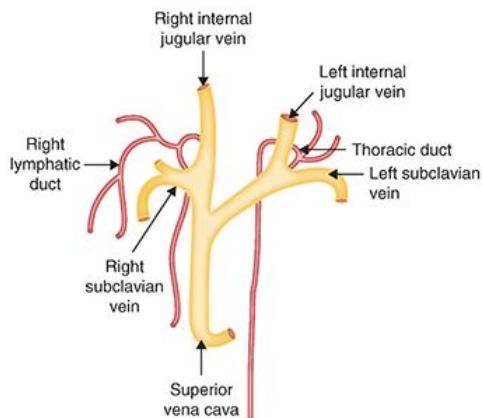


FIGURE 14.20 Depiction of the thoracic duct and right lymphatic duct as they enter the venous system.

Peripheral lymph vessels are small, difficult to identify, and contain flaplike valves between endothelial cells that open toward the interior, allowing the unimpeded entrance of interstitial fluid and proteins but preventing backflow.

Formation and Flow of Lymph

Lymph is interstitial fluid that flows into lymphatic vessels. The protein concentration of peripheral lymph is about 1.8 g/dL, whereas lymph from the gastrointestinal tract and liver contains 2 to 3 times this concentration of protein. The lymphatic system is one of the major channels for absorption of nutrients, especially fat, from the gastrointestinal tract. Bacteria that enter lymph vessels are removed and destroyed by lymph nodes.

Flow of lymph through the thoracic duct is about 100 mL per hour. A decrease in the normally negative value of interstitial fluid pressure increases the flow of interstitial fluid into terminal lymph vessels and consequently increases the rate of lymph flow. For example, at 0 mm Hg interstitial fluid pressure, the rate of lymph flow is increased 10 to 50 times compared with flow at an average interstitial fluid pressure of -6.3 mm Hg. Skeletal muscle contraction and passive movements of the extremities facilitate flow of lymph. For example, during exercise, lymph flow is increased up to 14 times that present at rest. Elevations in CVP can impair the return of lymph to the central circulation.

Edema

Edema is the presence of excess interstitial fluid in peripheral tissues that results from the inability of lymph vessels to adequately transport fluid. This may occur due to damage or obstruction of lymphatic vessels, excessive fluid administration, capillary fluid leakage due to increased permeability, low serum protein concentration, or elevated CVP. Peripheral edema most common in dependent areas may be accompanied by

accumulation of fluid in potential spaces such as the pleural cavity, pericardial space, peritoneal cavity, and synovial spaces. Excessive fluid in the peritoneal space—one of the spaces most prone to develop edema fluid—is called **ascites**. The peritoneal cavity is susceptible to the development of edema fluid because any increased pressure in the liver, such as occurs in cirrhosis or cardiac failure, causes transudation of protein-containing fluids from the surface of the liver into the peritoneal cavity.

Pulmonary Circulation

The pulmonary circulation is a low-pressure, low-resistance system in series with the systemic circulation. Pulmonary arteries have thinner walls and less smooth muscle than systemic arteries, and a relative lack of basal tone likely due to a predominance of endogenous vasodilators. Pulmonary vascular resistance is approximately one-tenth that of systemic resistance.

The volume of blood flowing through the lungs and systemic circulation is essentially identical. Blood passes through pulmonary capillaries in about 1 second, during which time it is oxygenated and carbon dioxide is removed.

Anatomy

Anatomically, the right ventricle is semilunar in shape, wrapped around the medial aspect of the left ventricle. The thickness of the right ventricle is one-third that of the left ventricle, as it normally generates pressures approximately 25% that of the left side.

The pulmonary artery extends only about 4 cm beyond the apex of the right ventricle before division into the right and left main pulmonary arteries. The pulmonary artery is a thin structure with a wall thickness about twice that of the vena cava and one-third that of the aorta. The large diameter and distensibility of the pulmonary arteries allows the pulmonary circulation to easily accommodate the stroke volume of the right ventricle. Pulmonary veins, like pulmonary arteries, are large in diameter and highly distensible. Pulmonary capillaries supply the estimated 300 million alveoli, providing a gas exchange surface of 70 m^2 .

Pulmonary blood vessels are innervated by the sympathetic nervous system, but the density of these fibers is less than in systemic vessels. α -Adrenergic stimulation from norepinephrine produces vasoconstriction of the pulmonary vessels, whereas β -adrenergic stimulation, as produced by isoproterenol, results in vasodilation. Parasympathetic nervous system fibers from the vagus nerves release acetylcholine, which produces vasodilation of pulmonary vessels. Despite the presence of autonomic nervous system innervation, the resting vasomotor tone is minimal, and the larger pulmonary vessels are almost maximally dilated in the normal resting state. Indeed, overall regulation of pulmonary blood flow is passive, with local adjustments of perfusion relative to ventilation being determined by local oxygen tension.

The diameter of thin-walled alveolar vessels changes in response to alterations in the transmural pressure (intravascular pressure minus alveolar pressure). If alveolar pressure exceeds intravascular pressure as occurs in nondependent regions of the lungs during positive pressure ventilation, pulmonary capillaries collapse and blood flow ceases. The size of larger vessels embedded in the lung parenchyma (extra-alveolar vessels) largely depends on lung volume. For example, resistance to flow through these vessels decreases as lung volumes increase because these vessels are tethered to the surrounding tissue ([Figure 14.21](#)). However, the largest pulmonary vessels, those at the hilum of the lung, vary in size in response to changes in intrapleural pressure.

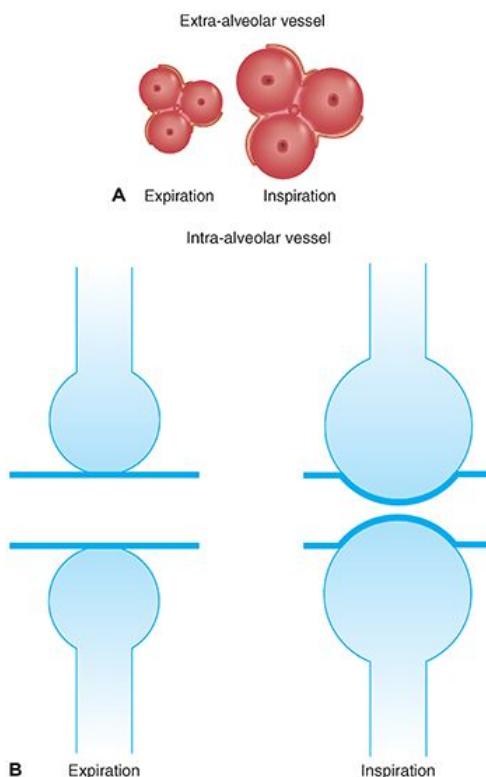


FIGURE 14.21 A, Schematic illustration of the effect of lung inflation on an extra-alveolar vessel surrounded by three alveoli. Extra-alveolar vessels are tethered by surrounding lung parenchyma and increase in caliber with lung inflation. B, Schematic illustration of an intra-alveolar vessel adjacent to two alveoli. Intra-alveolar vessels are compressed during lung inflation.

Bronchial Circulation

Bronchial arteries from the thoracic aorta supply oxygenated blood to supporting tissues of the lungs, including connective tissue and airways. After bronchial arterial blood has passed through supporting tissues, the majority of it empties into pulmonary veins and enters the left atrium rather than passing back to the right atrium. The entrance of deoxygenated blood into the left atrium dilutes oxygenated blood and accounts for an anatomic shunt that is equivalent to an estimated 1% to 2% of the cardiac output. This anatomic shunt plus a part of coronary blood flow which drains directly into the left side of the heart are the reasons the cardiac output of the left ventricle slightly exceeds that of the right ventricle.

Pulmonary Lymph Vessels

Pulmonary lymph vessels extend from all the supportive tissues of the lung to the hilum of the lung and then to the thoracic duct. Pulmonary lymphatic flow facilitates the removal of edema fluid from alveolar spaces. As lymph ultimately drains into the central venous circulation, lymph flow is reduced by elevated venous pressure.

Particulate matter entering the alveoli is also eventually removed by lymph vessels.

Pulmonary Vascular Pressure

The normal pressure in the pulmonary artery is about 22/8 mm Hg, with a mean pulmonary artery pressure of 13 mm Hg ([Figure 14.22](#)).⁴ The mean pulmonary capillary pressure is about 10 mm Hg, and the mean pressure in the pulmonary veins is about 4 mm Hg, such that the pressure gradient across the pulmonary circulation is only 9 mm Hg. The resistance to blood flow in the pulmonary circulation is about one-tenth the resistance in the systemic circulation.

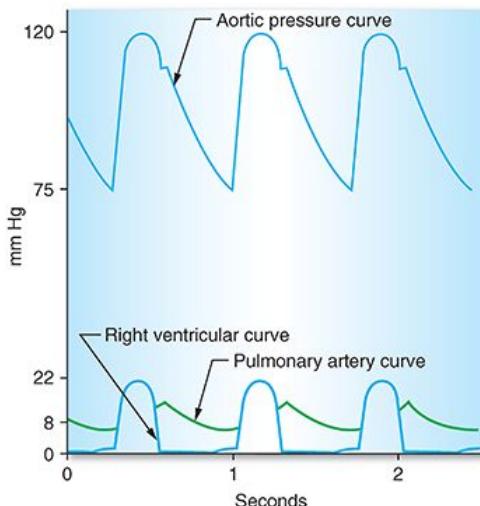


FIGURE 14.22 Comparison of intravascular pressures in the systemic and pulmonary circulations. Reprinted from Guyton AC, Hall JE. Textbook of Medical Physiology. 10th ed. Philadelphia, PA: W.B. Saunders; 2000. Copyright © 2000 Elsevier. With permission.

Pulmonary artery pressure is not typically influenced by left atrial pressures of less than 7 mm Hg. However, when left atrial pressure exceeds approximately 7 mm Hg, previously collapsed pulmonary veins are expanded, and pulmonary artery pressure increases in parallel with increases in left atrial pressure. In the absence of left ventricular failure, even marked increases in systemic vascular resistance do not cause the left atrial pressure to increase significantly. Consequently, the right ventricle continues to eject its stroke volume against a normal pulmonary artery pressure despite increased workloads imposed on the left ventricle. Accordingly, the right ventricular stroke volume is not measurably altered by changes in systemic vascular resistance unless the left ventricle fails.

Should the left ventricle fail, left atrial pressures can increase to greater than 15 mm Hg. Mean pulmonary artery pressures also increase, placing an increased workload on the right ventricle. If this occurs acutely, the right ventricle may also fail as it may not be able to generate an adequate stroke volume due to its structure (see earlier discussion). If pulmonary artery pressures rise gradually over time, the right ventricle may adapt with remodeling and dilation but will eventually begin to fail.

Measurement of Left Atrial Pressure

The left atrial pressure can be estimated by inserting a balloon-tipped catheter into a small pulmonary artery (ie, a pulmonary artery catheter placed in a major vein and advanced through the right heart to the pulmonary artery).

When the balloon is temporarily inflated and the vessel is completely occluded, a stationary column of blood is created distal to the catheter tip. As a result, the pressure measured immediately distal to the balloon is equivalent to that downstream in the pulmonary veins. This measurement is termed the **pulmonary artery occlusion pressure** (PAOP) and is usually 2 to 3 mm Hg higher than left atrial pressure. If the balloon is deflated, flow will resume and the pulmonary artery end diastolic pressure can be measured. This measurement correlates with the PAOP in the absence of pulmonary hypertension. A number of conditions can however make measurement of the PAOP unreliable, including where in the lung the tip of the catheter resides, the presence of high positive end-expiratory pressure, and vascular conditions making the PAOP higher than the LA pressure such as precapillary pulmonary hypertension or mitral valve stenosis.

Interstitial Fluid Space

The interstitial fluid space in the lung is minimal, and a continual negative pulmonary interstitial pressure of about -8 mm Hg dehydrates interstitial fluid spaces of the lungs and keeps the alveolar epithelial membrane in close approximation to the capillary membranes. As a result, the diffusion distance between gas in the

alveoli and the capillary blood is minimal, averaging about 0.4 micron. Negative pressure in pulmonary interstitial spaces draws fluid from alveoli through alveolar membranes and into the interstitium, keeping the alveoli dry. Mean pulmonary capillary pressure is about 10 mm Hg, whereas plasma colloid osmotic pressure is about 28 mm Hg. This net pressure gradient of about 18 mm Hg discourages the movement of fluid out of capillaries, decreasing the likelihood of pulmonary edema.

Pulmonary Blood Volume

Blood volume in the lungs is about 450 mL. Of this amount, about 70 mL is in capillaries and the remainder is divided equally between pulmonary arteries and veins. Cardiac failure or increased resistance to flow through the mitral valve causes pulmonary blood volume to increase.

Cardiac output can increase nearly 4 times before pulmonary artery pressure becomes increased ([Figure 14.23](#)).⁴ This reflects the distensibility of the pulmonary arteries and opening of previously collapsed pulmonary capillaries. The ability of the lungs to accept greatly increased amounts of pulmonary blood flow, as during exercise, without excessive increases in pulmonary artery pressures is important in preventing development of pulmonary edema or right ventricular failure.

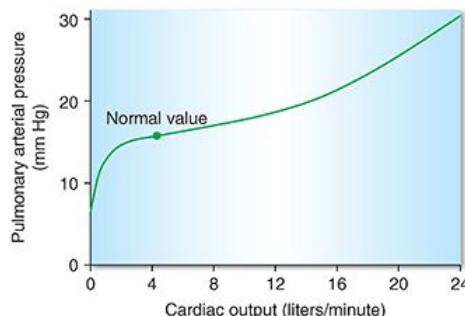


FIGURE 14.23 Cardiac output can increase nearly fourfold without greatly increasing the pulmonary arterial pressure. *Reprinted from Guyton AC, Hall JE. Textbook of Medical Physiology. 10th ed. Philadelphia, PA: W.B. Saunders; 2000. Copyright © 2000 Elsevier. With permission.*

Pulmonary blood volume can increase up to 40% when an individual changes from the standing to the supine position. This sudden shift of blood from the systemic circulation to pulmonary circulation is responsible for the decrease in vital capacity in the supine position and the occurrence of orthopnea in the presence of left ventricular failure.

Pulmonary Blood Flow and Distribution

Optimal oxygenation depends on matching ventilation to pulmonary blood flow.³¹ Shunt occurs in lung areas that are perfused but inadequately ventilated, whereas dead space ventilation occurs in lung areas that are ventilated but inadequately perfused ([Figure 14.24](#)). Although the lungs are innervated by the autonomic nervous system, it is doubtful that neural influences exert a major effect in the normal control of pulmonary blood flow. There is no doubt, however, that decreases in PaO_2 cause increases in pulmonary artery and right ventricular pressures.

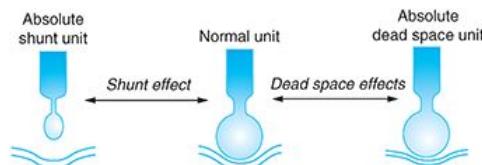


FIGURE 14.24 Gas exchange is maximally effective in normal lung units with optimal ventilation-perfusion (V/Q) relationships. The continuum of V/Q relationships is depicted by the ratios between normal and absolute shunt or dead space units.

Clinically, segmental pulmonary blood flow can be studied by intravenous injection of radioactive xenon while monitoring is performed externally over the chest with radiation detectors. Xenon rapidly diffuses from capillaries into alveoli, and radioactivity is detected early in well-perfused regions of the lung.

Endothelial Regulation of Pulmonary Blood Flow

Active vasodilation is crucial to the maintenance of the low resting tone of the normal pulmonary circulation. The pulmonary vascular endothelium is responsible for the synthesis and secretion of various compounds that regulate smooth muscle activity in the pulmonary circulation. The primary vasodilatory compounds are NO and prostacyclin. The predominant influence of a healthy pulmonary endothelium is to reduce pulmonary vascular tone. Endothelin is also released by the pulmonary endothelium and may have both a constrictive or dilatory effect depending on the circumstances. There are several negative feedback mechanisms in effect that regulate vascular tone. The synthesis and release of NO, prostacyclin, ET-1, and other vasoactive compounds are integrated into a system that optimizes pulmonary vascular tone and facilitates local control of ventilation-perfusion matching.³²

Nitric Oxide and Prostacyclin

NO is produced in endothelial cells of the pulmonary vasculature and similar to the systemic circulation plays a major role in maintaining low vascular tone. It is the most widely studied potent pulmonary vasodilator, produced via the action of cNOS, which oxidizes L-arginine into L-citrulline and NO; the NO then activates soluble guanylate cyclase in surrounding smooth muscle, which produces cyclic guanylate monophosphate, reducing intracellular calcium and myofilament sensitivity to calcium. The activity of cNOS is rapidly up- or downregulated and produces picomolar amounts of NO in response to stimuli such as shear stress and local oxygen tension. In pathologic states, another NOS isoform, iNOS, produces considerably larger quantities of NO but takes longer to upregulate and downregulate. The iNOS is located in vascular smooth muscle cells and inflammatory macrophages. Inflammatory mediators are potent upregulators of iNOS activity. The NO induces vasorelaxation by stimulating the production of cyclic guanosine monophosphate (cGMP) by the enzyme guanylate cyclase. The cGMP is promptly metabolized by phosphodiesterases. Increased cGMP production appears to stimulate phosphodiesterase upregulation, thus causing accelerating cGMP clearance. Indeed, phosphodiesterase upregulation may be partly responsible for suboptimal responses to inhaled NO (iNO) and for rebound pulmonary hypertension after NO withdrawal. Type V phosphodiesterase is the predominant enzyme type in the pulmonary circulation. Selective inhibitors of type V phosphodiesterase such as sildenafil can both selectively decrease pulmonary vascular resistance when given alone and significantly potentiate the effects of iNOS and prostacyclin.

Whereas oral agents that stimulate the production of cGMP (eg, riociguat) or inhibit its breakdown (eg, sildenafil) are useful for outpatient management of pulmonary hypertension,³³ iNO is only available for clinical use in the critical care or operating room setting. With its very short half-life, it has no systemic effects and is truly a selective pulmonary vasodilator. It is delivered only to ventilated alveoli and therefore improves oxygenation by better matching blood flow to ventilation. Its only US Food and Drug Administration-approved indication is for neonatal hypoxic respiratory failure (with proven outcome benefit), but iNO is also widely used in adult settings of severe refractory hypoxemia, pulmonary hypertension not related to left heart failure, and in right heart failure. It is used in the setting of heart and lung transplantation for both its effect on oxygenation and reduction in pulmonary artery pressure.³⁴

Prostacyclin or PGI₂ is one of a number of prostaglandins produced in endothelial cells; PGI₂ activates adenylate cyclase causing increased adenosine 3',5'-cyclic adenosine monophosphate release, promoting relaxation of vascular smooth muscle. Phosphodiesterase inhibitors reduce the breakdown of cyclic adenosine monophosphate; therefore, oral phosphodiesterase inhibitors increase the vasodilating actions of both iNO and PGI₂. Intravenous administration of PGI₂ through a dedicated central catheter has been used for chronic use in severe pulmonary hypertension (not due to left heart failure) for some time; it is not, however, a selective pulmonary dilator and must be initiated and uptitrated in a monitored setting. As a nonselective dilator, it may worsen ventilation-perfusion mismatch, and abrupt withdrawal can result in severe increases in

pulmonary artery pressures and right heart failure. When aerosolized, PGI₂ becomes more selective, but its elimination is slower than that of iNO, and systemic effects are possible. The PGI₂ has been employed in hypoxic respiratory failure and similar perioperative settings to those described earlier with iNO; published evaluations of the two drugs suggest they are similar in efficacy, and there is no benefit to administering both at the same time. Whereas its administration is a little more complex, aerosolized PGI₂ is significantly less expensive than iNO. Both are generally administered to intubated patients, but both can be administered through facemask or nasal cannula as well, most often as the patient is recovering from their condition and being weaned from the drugs. Dosage in this setting is of course much less predictable than when the patient is intubated. Other formulations or analogues of PGI₂ are used in outpatient therapy but less often in the perioperative or critical care setting.

Endothelin

Endothelin (ET-1) is a potent endogenous vasoconstrictor made in endothelial cells, which then acts on specific receptors on vascular smooth muscle cell membranes. Some types of pulmonary hypertension may be related to either increased production or reduced elimination of ET-1. The oral drug bosentan is an endothelin receptor antagonist used in outpatient treatment of pulmonary hypertension.³³

Hypoxic Pulmonary Vasoconstriction

Alveolar hypoxia ($\text{PaO}_2 < 70 \text{ mm Hg}$) evokes vasoconstriction in the pulmonary arterioles supplying these alveoli. The net effect is to divert blood flow away from poorly ventilated alveoli. As a result, the shunt effect is minimized, and the resulting PaO_2 is maximized. The mechanism for hypoxic pulmonary vasoconstriction is presumed to be locally mediated, as this response occurs in isolated and denervated lungs as well as intact lungs. Indeed, this vasoconstrictor response is apparent in isolated pulmonary artery strips and isolated smooth muscle cells. There are probably multiple mechanisms responsible for hypoxic pulmonary vasoconstriction, and these mechanisms likely differ during acute and chronic responses. The suppression of endothelial release of the potent vasodilator NO is likely an important element of both the acute and chronic response. A crucial component of the acute response is the inhibition of potassium channels that leads to membrane depolarization. Membrane depolarization increases calcium influx, which in turn activates the intracellular contractile response. Chronic vascular responses to hypoxia may be, in part, mediated by endothelin release and eventually involve vascular remodeling, eventually leading to irreversible increases in pulmonary vascular resistance (pulmonary hypertension).

Drug-induced inhibition of hypoxic pulmonary vasoconstriction could result in unexpected decreases in PaO_2 in the presence of lung disease. Potent vasodilating drugs such as nitroprusside and nitroglycerin may be accompanied by decreases in PaO_2 attributed to this effect.³⁵ Other antihypertensive agents such as angiotensin-converting enzyme inhibitors, calcium antagonists, and likely all arterial vasodilators may reduce hypoxic pulmonary vasoconstriction and worsen oxygenation.

Although animal studies suggest that potent inhaled anesthetic agents inhibit hypoxic vasoconstriction in a dose-dependent manner, in clinically relevant concentrations, these findings have not been supported by clinical studies in patients (Figure 14.25).^{36,37} The present consensus is that potent volatile anesthetics are acceptable choices for thoracic surgery requiring one-lung ventilation, particularly in view of the beneficial effects of these drugs on bronchomotor tone and their high potency that permits delivery of maximal concentrations of oxygen.³⁸

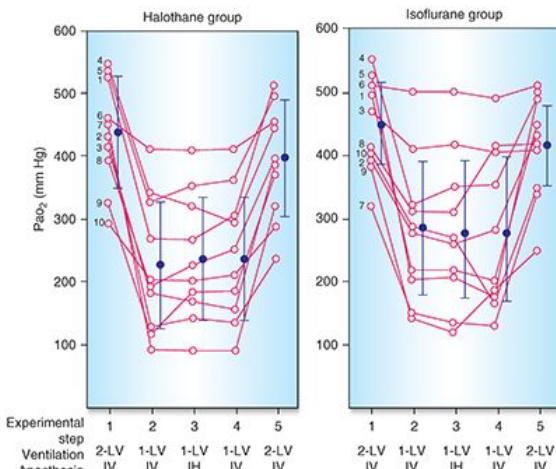


FIGURE 14.25 PaO_2 was measured during two-lung ventilation (2-LV) and then during one-lung ventilation (1-LV) in patients anesthetized with fentanyl and diazepam without halothane or isoflurane (experimental steps 2 and 4) and with halothane or isoflurane (experimental step 3). Addition of halothane or isoflurane (about 1.2 minimum alveolar concentration) does not alter the PaO_2 , suggesting these drugs do not inhibit hypoxic pulmonary vasoconstriction. Clear circles are individual patient data and closed circles are mean \pm standard deviation for each group. *Reprinted with permission from Rogers SN, Benumof JL. Halothane and isoflurane do not decrease PaO_2 during one-lung ventilation in intravenously anesthetized patients. Anesth Analg. 1985;64(10):946-954. Copyright © 1985 International Anesthesia Research Society.*

Carbon Dioxide and Acid–Base Effect

Both respiratory and metabolic acidosis cause pulmonary vasoconstriction in the absence of hypoxemia.³⁹ Where there is hypoxic vasoconstriction, however, hypercarbia or acidosis may have a vasodilating effect. Hypocarbia and metabolic alkalosis cause pulmonary vasodilation, which can moderate hypoxic vasoconstriction. As changes in carbon dioxide and acid–base status are common during anesthesia, close attention needs to be paid when managing patients with pulmonary hypertension.

Effect of Breathing

During spontaneous respiration, venous return to the heart is increased due to contraction of the diaphragm and abdominal muscles, which decreases intrathoracic pressure. The resulting augmented blood flow to the right atrium increases right ventricular stroke volume. In contrast to spontaneous breathing, positive pressure ventilation increases intrathoracic pressure and thus impedes venous return to the heart and decreases right ventricular stroke volume.

Regional Blood Flow in the Lungs

Although traditional teaching has focused on the gravitational effect of blood flow within the lungs, more recent work has demonstrated that the gravitational “zone”⁴⁰ (**Figure 14.26**) has a relatively minor role in blood flow distribution. On average, pulmonary blood flow is greater in areas of the lung below the heart as compared to those above the heart,⁴¹ but measurements have demonstrated greater variation from spot to spot in any isogravitational plane than there is on average from the top of the lung to the bottom. Indeed, only 25% of the variability in pulmonary blood flow is accounted for by gravitational effects. Furthermore, the local differences in flow at any isogravitational level are fairly constant over time, suggesting that approximately 75% of the distribution of pulmonary blood flow is determined by the branching structure of the pulmonary vascular tree.

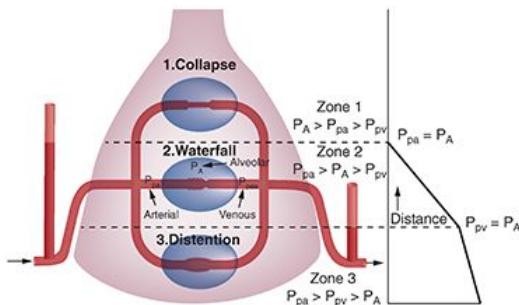


FIGURE 14.26 The lung is divided into three pulmonary blood flow zones reflecting the impact of alveolar pressure (P_A), pulmonary artery pressure (P_{pa}), and pulmonary venous pressure (P_{pv}) on the caliber of pulmonary blood vessels. *Reprinted with permission from West JB, Dollery CT, Naimark A. Distribution of blood flow in isolated lung: relation to vascular and alveolar pressures. J Appl Physiol. 1964;19(4):713-724.* Copyright © 1964 the American Physiological Society.

Pulmonary Circulatory Pathology

Pulmonary Edema

Pulmonary edema is present when there are excessive quantities of fluid either in pulmonary interstitial spaces or in alveoli. Mild degrees of pulmonary edema may be limited to only an increase in the interstitial fluid volume. The alveolar epithelium, however, is not able to withstand more than a modest increase in interstitial fluid pressure before fluid spills into alveoli. Dehydrating forces of the colloid osmotic pressure of the blood in the lungs provide a large safety factor against development of pulmonary edema. In humans, plasma colloid osmotic pressure is about 28 mm Hg, so pulmonary edema rarely develops below a pulmonary capillary pressure of 30 mm Hg. The most common cause of acute pulmonary edema is greatly increased pulmonary capillary pressure resulting from left ventricular failure, and the lymphatic flow cannot adequately remove the increased fluid.

During chronic increases of left atrial pressure, pulmonary edema may not occur despite pulmonary capillary pressures as high as 45 mm Hg. Enlargement of the pulmonary lymph vessels allowing lymph flow to increase up to 20 times is the most likely reason pulmonary edema does not occur in the presence of chronically increased left atrial pressures. At the other end of the spectrum, a transplanted lung does not have any lymphatic drainage and is acutely sensitive to fluid overload or increased in left atrial pressure.

Pulmonary edema can also result from local capillary damage that occurs with inhalation of acidic gastric fluid or irritant gases, such as smoke. The result is rapid transudation of fluid and proteins into alveoli and interstitial spaces. This is called **permeability pulmonary edema** to distinguish it from “hydrostatic” pulmonary edema, which is due to increased pulmonary capillary pressure. In either case, increased interstitial fluid and fluid-filled alveoli interfere with gas exchange, decrease lung compliance, and result in an increase in the work of breathing.

Pulmonary Embolism

Embolism of venous clots to the lungs may be chronic with small emboli or acute with massive embolus. Total blockage of a major branch of a pulmonary artery by an embolus is usually not immediately fatal because other lung regions may be able to accommodate all the pulmonary blood flow, but major emboli may result in right ventricular strain and failure. Tachypnea and dyspnea are characteristic responses in awake patients experiencing pulmonary embolism; in the anesthetized patient, an acute decrease in end-tidal carbon dioxide may occur due to a sudden increase in dead space (loss of perfusion but not ventilation to major part of the lung). Depending on the circumstance, anticoagulation, thrombolysis, or pulmonary embolectomy may be indicated.

Pulmonary Hypertension

The World Health Organization has classified pulmonary hypertension according to etiology (**Table 14.8**),⁴² but the hemodynamic diagnosis in all causes is made when the sustained mean pulmonary artery pressure is above 25 mm Hg. The cause may be “primary” or idiopathic (type 1) or in association with other disease (other types). As mentioned earlier, gradual increases in pulmonary artery pressure may be tolerated by the right heart, but with progressive increases in pressure, right ventricular failure will eventually occur. In addition, many of the causes of pulmonary hypertension are associated with the development of hypoxemia. As the pathophysiologies of the different types of pulmonary hypertension are quite different, so are the treatments. As hypoxemia is a feature of all types for the disease, especially in the later stages, oxygen therapy is generally indicated. Similarly, thrombotic disease can occur even when this is not the primary cause (type 4), so anticoagulation may be indicated. Where left heart failure is the cause (type 2), pulmonary vasodilator therapy may actually worsen the heart failure; treatment must directly address left heart function. Similarly, with thromboembolic disease, thromboendarterectomy and anticoagulation rather than pulmonary dilators are the mainstay of treatment. Chronic intravenous therapy with PGI₂ or intermittent aerosol (inhaler) treatment with a prostacyclin analogue are generally used in severe type 1 disease.³³ As described earlier, acute treatment with iNO or continuous aerosolized PGI₂ is reserved for severe disease in the inpatient with hypoxic respiratory failure in association with pulmonary hypertension and right heart dysfunction. When medical treatment fails, ultimately lung or heart-lung transplant may be required.

TABLE 14.8

Classification of pulmonary hypertension^a

I	Pulmonary arterial hypertension (PAH) Idiopathic PAH (majority) and heritable PAH Drug- and toxin-induced PAH Connective tissue disease–associated PAH HIV-associated PAH Portal hypertension–associated PAH Congenital heart diseases Schistosomiasis
II	Pulmonary hypertension due to left heart disease LV systolic and diastolic dysfunction Valvular disease Congenital/acquired left heart inflow/outflow tract obstruction Developmental lung diseases
III	Pulmonary hypertension due to lung diseases or hypoxia COPD, ILD, mixed restrictive/obstructive pattern disease Sleep-disordered breathing and alveolar hypoventilation disorders Chronic exposure to high altitude Developmental lung diseases
IV	Chronic thromboembolic pulmonary hypertension
V	Pulmonary hypertension due to multifactorial mechanisms Hematologic: chronic anemia, myeloproliferative disorders, splenectomy Systemic: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis Metabolic: glycogen storage disease, Gaucher disease, thyroid disease Others: tumor obstruction, fibrosis mediastinitis

Abbreviations: COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; ILD, interstitial lung disease; LV, left ventricular.

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Cardiac Physiology*

Updated by: Teresa A. Mulaikal • Andrea N. Miltiades • Sumeet Goswami • Bessie Kachulis

The heart has four chambers and can be characterized as two pumps connected in series, each composed of an atrium and a ventricle. The atria function primarily as conduits to the ventricles, but they also contract weakly to facilitate movement of blood into the ventricles during the filling phase, diastole. The ventricles serve as pumps during systole to supply the main force that propels blood through the systemic and pulmonary circulations. Specialized excitatory and conductive fibers in the heart maintain cardiac rhythm and transmit action potentials through cardiac muscle to initiate contraction. Because the heart is coupled to two circulations in series, its function is influenced by the characteristics of both.

Cardiac Anatomy

Pericardium

The pericardium is a fibrous sac that contains the heart and the proximal portions of great vessels. It consists of two layers: the fibrous and serosal pericardium. The fibrous layer is fibrocollagenous and is continuous superiorly with the adventitia of the great vessels and the pretracheal fascia and inferiorly with the diaphragm. Anteriorly, the fibrous layer attaches to the sternum through the sternopericardial ligaments. The aorta, pulmonary arteries, and pulmonary veins also receive extensions from the fibrous pericardium. The serosal layer of the pericardium is enclosed within the fibrous pericardium and consists of a single, continuous membrane that is divided into two parts: the visceral and the parietal pericardium. The visceral layer surrounds the heart and the great vessels and is reflected on to the parietal layer that lines the inner surface of the fibrous pericardium.¹⁻³

The potential space between visceral and parietal pericardium normally contains 15 to 35 mL of pericardial fluid. The inelastic nature of the pericardium limits acute dilation of the heart and enhances the resulting mechanical interaction of the four cardiac chambers. Acutely, the pericardium can only accommodate a small amount of pericardial fluid without changes in intrapericardial pressure. Once the amount of pericardial fluid exceeds a limited reserve capacity, the intrapericardial pressure increases steeply with small amounts of pericardial fluid, leading to tamponade physiology. Chronically, the pericardium can accommodate a large amount of fluid without causing tamponade because its size and compliance increase in compensation.¹⁻³

Heart

The heart consists of four chambers. The right atrium receives deoxygenated blood from the superior vena cava, the inferior vena cava, the coronary sinus (CS), and Thebesian cardiac veins. It pumps deoxygenated blood into right ventricle through the tricuspid valve. The right atrium is divided into three regions: the posteriorly located smooth-walled venous component, the anteriorly located vestibule of the tricuspid valve, and the right auricle. The venous component, or the sinus venosum, receives the venae cavae and the CS. The venous part of the atrium is separated from atrium proper and the auricle by a ridge of muscle called the **crista terminalis**. The pectinate muscles are muscular trabeculae that extend anterolaterally from crista terminals into the auricle. Anterior to the orifice of inferior vena cava is the eustachian valve, which in the fetal circulation directs oxygen-rich blood from placenta into left atrium through the foramen ovale of atrial septum. The fossa ovalis is the thin part of the atrial septum, above and to the left of the orifice of inferior vena cava. The vestibule of the tricuspid valve is the anteroinferior portion of right atrium.¹⁴

The atrioventricular (AV) valvular complex, both on the right and the left side (tricuspid and mitral valve), consists of the annulus, the leaflets, the chordae tendineae, and the papillary muscles. The tricuspid valve is so named as it has three leaflets, one each located anterosuperiorly, septally, and inferiorly. The

chordae tendineae are fibrous collagenous structures that support the leaflets of tricuspid and mitral valves during systole. True chordae arise usually from the papillary muscles or from the ventricular free wall and the septum. There are three papillary muscles in the right ventricle: two larger, located in the anterior and posterior positions of the right ventricle, and a smaller muscle arising from the ventricular septum.^{1,4}

The right ventricle consists of the inlet adjacent to the tricuspid valve and the apex, both of which are trabeculated. The smooth-walled infundibulum or the outlet connects to the pulmonic valve. The inlet and outlet components are separated by a transverse ridge of muscle called the supraventricular crest or the crista supraventricularis. The many muscular ridges and protrusions into the inner surface of the inlet and apex are known as trabeculae carneae. The septal band or the septomarginal trabecula reinforces the septal surface; at the apex, it supports the anterior papillary muscle, from where it crosses to the parietal wall of the ventricle as the moderator band. The pulmonic valve is located at the distal end of the infundibulum and consists of three semilunar cusps, an anterior, a right, and a left cusp.^{1,4}

The left atrium is normally smaller in size than the right but has thicker walls. The right atrium is anterior and somewhat to the right of the left atrium. The right and the left atrium are separated by the obliquely positioned atrial septum. The superior posterior aspect of the left atrium receives the pulmonary veins and forms the anatomic base of the heart. The left auricle is longer and narrower than the right auricle and is the only portion of the left atrium that is trabeculated.^{1,4}

The mitral valve apparatus consists of an orifice with an annulus, anterior and posterior leaflets, many chordae tendineae, and two papillary muscles. The anterior and posterior leaflets converge at the anterolateral and posteromedial commissures, each of which is associated with a papillary muscle. The anterior leaflet is semicircular and occupies one-third of the circumference, whereas the posterior leaflet is elongated and narrow and is attached to the remaining two-thirds of the annulus. The posterior leaflet is divided into three parts based on the presence of two indentations: a lateral P1, a central P2, and a medial P3 scallop. The segments of anterior leaflet opposing the posterior leaflet are similarly designated as A1, A2, and A3 scallop ([Figure 15.1](#)).⁵

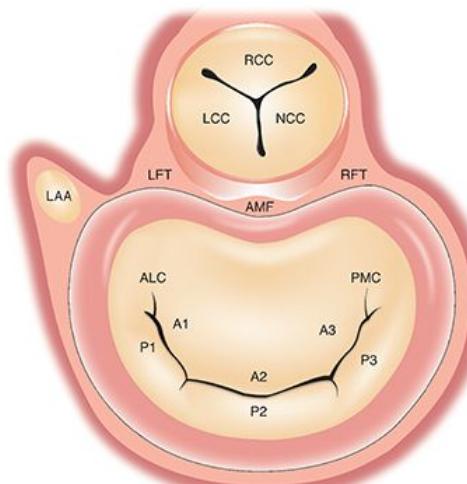


FIGURE 15.1 Representation of mitral valve anatomy.⁵ Anterior mitral valve leaflet with segments A1, A2, and A3; posterior mitral valve leaflet with scallops P1, P2, and P3. Abbreviations: ALC, anterolateral commissure; AMF, aortic-mitral fibrosa; LAA, left atrial appendage; LCC, left coronary cusp of aortic valve; LFT, left fibrous trigone; NCC, noncoronary cusp of aortic valve; PMC, posteromedial commissure; RCC, right coronary cusp of aortic valve; RFT, right fibrous trigone. Reprinted with permission from Debonnaire P, Palmen M, Marsan NA, et al. Contemporary imaging of normal mitral valve anatomy and function. *Curr Opin Cardiol.* 2012;27(5):455-464.

The subvalvular apparatus consists of chordae tendineae and the papillary muscles. The chordae tendineae attach to the edges of mitral leaflets or to its ventricular surface. The left ventricle has two papillary

muscles: the anterolateral papillary muscle and the posteromedial papillary muscle. The chordae tendineae arise from the papillary muscle and attach to the ipsilateral half of anterior and posterior mitral leaflets.¹⁴

The left ventricle is a cone-shaped structure that is longer and narrower than the right ventricle. In the long axis, it descends forward and to the left from its base at the AV groove to form the cardiac apex. Its walls are normally about 2 to 3 times thicker than the right ventricle. It consists of the inlet region, the apical trabecular component, and the smooth-walled outflow tract. Unlike the valvular orifices of the right ventricle, the orifices of the aortic and mitral valve are in fibrous continuity. The left ventricular outflow tract (LVOT) ends at the aortic valve. The aortic valve consists of three semilunar cusps that are supported within the three aortic sinuses of Valsalva. The cusps and the sinuses are called **left**, **right**, and **noncoronary**.¹⁴

The Coronary Circulation

A unique feature of the coronary circulation is that the heart requires a continuous delivery of oxygen by coronary blood flow to function. At rest, the myocardium extracts about 75% of the oxygen delivered by coronary blood flow more than any other tissue in the body. So whenever myocardial oxygen demand increases, as with exercise, the coronary arteries must dilate to increase blood flow and oxygen delivery to meet the demand, or ischemia results. This coronary artery dilation is mediated through the local release of vasodilator substances within the myocardium.^{6,7}

The right (RCA) and the left (LCA) coronary arteries arise respectively from the upper part of the right and the left CS of Valsalva and are the first branches of the aorta ([Figure 15.2](#)). The RCA usually supplies most of the right ventricle, a small part of the diaphragmatic aspect of left ventricle, the right atrium, part of left atrium, and posteroanterior one-third of interventricular septum. The first segment of the RCA gives rise to right ventricular and atrial branches. The right ventricular branches are the right conus artery or the infundibular artery and the acute marginal arteries. The atrial branch in majority of the population is the artery to the sinoatrial (SA) node. The RCA passes directly into the right interventricular groove and descends to the right cardiac border, where it curves posteriorly and approaches the junction of interatrial and interventricular grooves (the crux of the heart) and gives rise to the posterior descending artery (PDA). Coronary artery dominance is defined by the artery that supplies the PDA. In 70% of the population, the PDA is supplied by the RCA, coronary circulation referred to as **right dominant**. In 10% of the population, the PDA is supplied by circumflex artery (Cx A) and is left dominant. In the remainder, the PDA is supplied by both the RCA and the Cx A, and the coronary circulation is considered codominant.^{1,6}

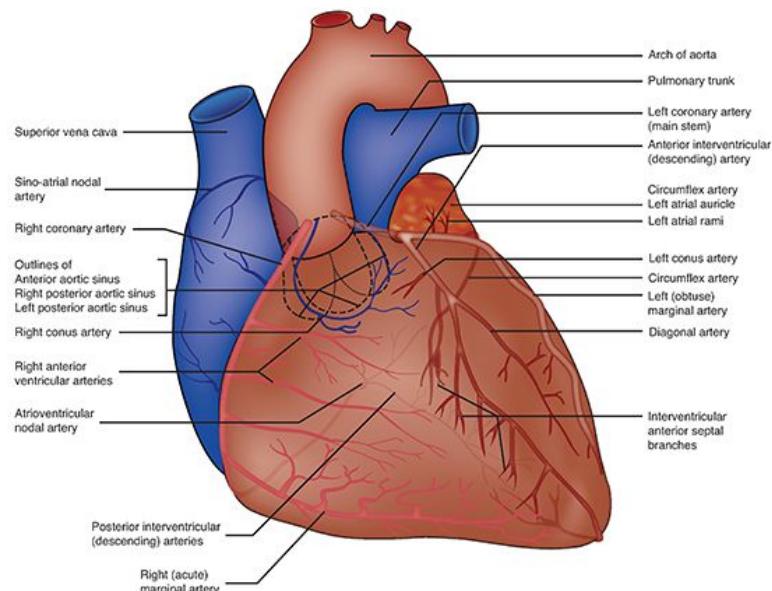


FIGURE 15.2 The coronary circulation.¹

The left main coronary artery usually supplies the free wall of the left ventricle, a narrow strip of the right ventricle anteriorly, the anterior two-thirds of ventricular septum, and most of left atrium. After arising from the left CS, the left main coronary artery passes to the left AV groove, where it branches into left anterior descending artery (LAD) and the CxA. The LAD, also known as **anterior interventricular artery**, runs in the anterior interventricular groove and gives off right and left diagonal and septal branches. The right diagonal branches are small and rare; the left diagonal arteries can vary in number anywhere from two to nine and cross the anterior surface of the left ventricle. The septal branches supply most of the interventricular septum. The first septal branch is usually targeted for ablation in interventional treatment for hypertrophic cardiomyopathy. The CxA curves left in AV groove giving rise to obtuse marginal branches extending over the posterolateral wall toward the apex. The CxA continues into the posterior part of the AV groove, usually terminating prior to the crux of the heart, but in 10% of individuals, it continues to supply the PDA.^{1,6}

The cardiac veins that run in AV and interventricular grooves drain a large part of coronary arterial blood into the right atrium via the CS. The great cardiac vein that accompanies the LAD is joined by the oblique vein of the left atrium in the left AV groove to become the CS. Prior to draining into the right atrium, the middle cardiac vein that runs in the inferior interventricular groove and small cardiac vein that runs in right AV groove drain into the CS.^{1,6}

The Cardiac Conduction System

The cardiac conduction system consists of the SA node, the AV node, the AV bundle also known as the **bundle of His**, the bundle branches, and the Purkinje fibers (**Figure 15.3**). The cardiac impulse is normally initiated by the SA node. This causes the atria to contract, first the right atrium followed by the left atrium. The blood supply to the SA node may be from either the RCA or the CxA.

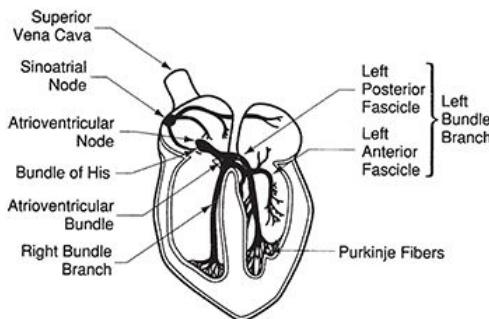


FIGURE 15.3 Cardiac conduction system.

From the SA node, the impulse is conducted to the AV node via the atrial myocardium. The AV node is located at the apex of region formed by the opening of the CS, the septal leaflet of the tricuspid valve, and the atrial septum, called the **triangle of Koch**. The AV node is supplied by the RCA in a large majority of population, in the rest by the CxA. The cardiac electrical impulse is delayed in the AV node about a fifth of a second before being conducted to the bundle of His and on to the ventricles, so that the atria contract just before the ventricles to augment end diastolic filling. The bundle of His branches into right and left bundle branches. The left bundle splits further into anterior and posterior fascicles. The bundle branches descend through the ventricular septum, where they continue on as the Purkinje fibers that end up directly stimulating the myocardium to contract. The bundle of His and bundle branches are insulated from the myocardium by a fibrous sheath, thus forming specialized network of conduction tissue. This functional organization results in a coordinated, synchronized contraction of the atria and ventricles, improving the efficiency of the heart.^{1,6,8,9}

Clinical Electrophysiology and Electrocardiogram

Body fluids are good electrical conductors, making it possible to record the sum of the action potentials of the cardiac cells on the surface of the body. Continuous monitoring of this electrocardiogram (ECG) during anesthesia is considered to be a standard of monitoring for all patients under the anesthesiologist's care. It is an essential tool for detecting myocardial ischemia, arrhythmias, and conduction system abnormalities.

Electrocardiogram Leads

The cardiac electrical activity is usually measured by electrodes placed on the skin. Bipolar leads consist of two electrodes: one positive and one negative. Unipolar leads consist of one positive electrode (exploring) and a composite pole that averages electrical activity from a number of other leads to zero potential, referred to as the **indifferent electrode**. Depolarization directed toward the positive electrode produces a positive deflection, whereas directed away from it produces a negative deflection. When the depolarization wave is perpendicular to the lead, a biphasic deflection is recorded ([Figure 15.4](#)). The 12-lead ECG consists of three bipolar standard limb leads, six unipolar precordial leads, and three unipolar augmented limb leads. The standard limb leads and the augmented limb leads record electrical impulses that flow in the frontal plane, whereas the precordial leads record impulses in the horizontal plane.

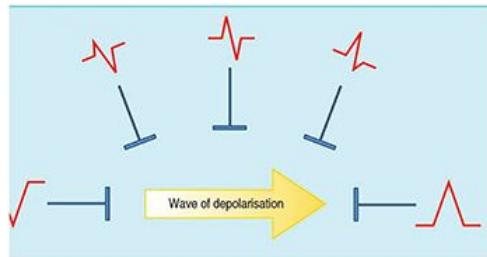


FIGURE 15.4 Wave of depolarization. Shape of QRS complex in any lead depends on orientation of that lead to vector of depolarization. *Reproduced from Meek S, Morris F. Introduction. I—leads, rate, rhythm, and cardiac axis. BMJ. 2002;324(7334):415-418 with permission from BMJ Publishing Group Ltd.*

Standard Limb Leads. The standard limb leads, named I, II, and III, record the potential difference between two points of the body ([Figure 15.5](#)). In lead I, the electrodes are placed on the left shoulder (positive) and right shoulder (negative). In lead II, the positive electrode is on the left leg and the negative is on the right shoulder. In lead III, the positive electrode is on the left leg and the negative on the left arm. The limb leads form the triangle of Einthoven, which is used together with the augmented limb leads to calculate the electrical axis of the heart in the frontal axis. The direction of the depolarization of the atria parallels lead II, resulting in a prominent P wave in this lead.

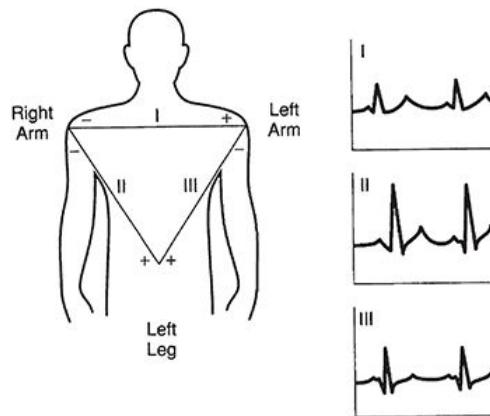


FIGURE 15.5 Standard limb leads of the electrocardiogram and typical recordings.

Augmented Limb Leads. Augmented leads are similar to the standard limb leads but are unipolar. Linking the three limb leads through equal resistances ($5,000 \Omega$), a central terminal is created with zero potential (Wilson central terminal). This is based on Einthoven theory that the R wave in lead II equals the sum of the R waves in leads I and III. The central terminal presents a stable reference potential point that is used to measure the varying potential at the exploring electrode ([Figure 15.6](#)). Goldberger modified the central terminal by

removing its link from the exploring electrode, achieving augmentation on the ECG deflections.¹⁰ The positive (exploring) electrode for augmented voltage right arm (aVR) is on the right shoulder; for augmented voltage left arm (aVL), on the left shoulder; and for augmented voltage foot (aVF), on the left leg.

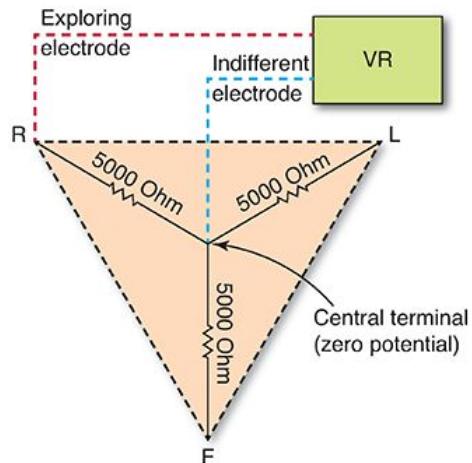


FIGURE 15.6 Unipolar limb lead circuit (VR).

Precordial Leads. The precordial leads (V_1-V_6) are unipolar leads that are placed on the chest wall, with the exploring electrode over one of six separate points (Table 15.1). The “indifferent” electrode is represented by the Wilson central terminal, which is the average of the standard limb leads and normally has zero potential. The proximity of the heart surface to the electrode allows for detection of relatively small abnormalities in the ventricles without augmentation. Electric current flow is normally from the base to the apex of the heart. Therefore, leads V_1 and V_2 , being near the base, record a negatively deflected QRS. Conversely, V_4 to V_6 , being nearer the apex, record a positively deflected QRS.

TABLE 15.1

Placement of precordial leads

V_1	Fourth intercostal space at the right sternal border
V_2	Fourth intercostal space at the left sternal border
V_3	Equidistant between V_2 and V_4
V_4	Fifth intercostal space in the left midclavicular line
V_5	Fifth intercostal space in the left anterior axillary line
V_6	Fifth intercostal space in the left midaxillary line

Electrocardiographic Axis of the Heart

The axis represents the overall direction of the electric impulse in the heart and is created by averaging all the action potentials. It is biased toward the left because of the larger muscle mass of the left ventricle compared to the right. The standard limb leads combined with the augmented limb leads form the hexaxial diagram, which is used to calculate the electrical axis of the heart on the frontal plane (Figure 15.7). This axis normally ranges between -30 and 90 degrees. Hypertrophy of the left ventricle shifts the axis to the left, and hypertrophy of the right shifts it to the right. Left axis deviation is defined as an axis less than -30 degrees and right axis deviation as more than 90 degrees. Abnormalities in the normal conduction pathway (blocks) in the heart also cause changes in the electrical axis.

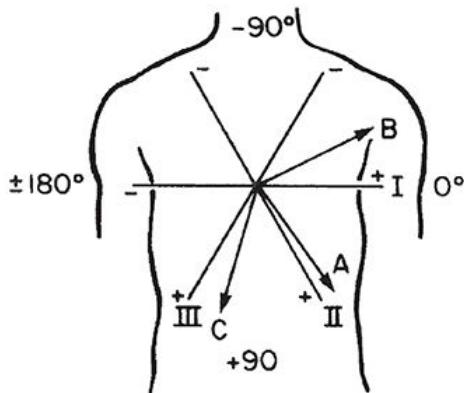


FIGURE 15.7 Electrical axis of the heart as determined from the standard limb leads of the electrocardiogram. In the normal heart, the electrical axis is approximately 59 degrees (A). Left axis deviation shifts the electrical axis to less than 0 degrees (B); right axis deviation is associated with an electrical axis of greater than 100 degrees.

Electrocardiogram Lead Systems

The three-lead system is the most basic ECG system. It consists of three electrodes, placed on the right arm, left arm, and left leg. It monitors electrical activity recorded by the bipolar standard limb leads (I, II, and III). Only one lead at a time is available. Two electrodes are used to form the selected lead, and the third becomes the ground. Although the three-lead ECG provides adequate monitoring for arrhythmias, its use for detection of myocardial ischemia is limited.

In the modified three-lead bipolar standard limb lead system, the electrodes are placed in different locations on the chest wall. This allows for improved detection of arrhythmias (taller P waves) and monitoring for ischemia of the heart surface closer to each exploring pole. In the central subclavicular lead system (SC_5), one electrode is placed under the right clavicle, one in the V_5 position, and the ground electrode on the left leg. Other modified systems include the modified central leads (MCL), central manubrial (CM_5), central back (CB_5), and central cardiac 5 (V_5) lead systems ([Figure 15.8](#)).

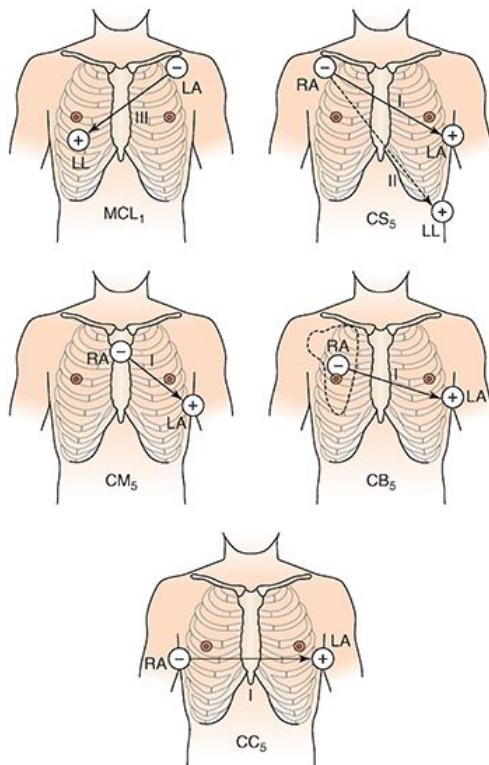


FIGURE 15.8 Modified bipolar standard limb lead system.

The 5-lead system uses 5 electrodes placed on the right arm, right leg, left arm, left leg, and one on the chest wall in any one position from V_1 to V_6 . Seven leads at a time may be monitored: 6 bipolar (I, II, III, aVR, aVL, aVF) and 1 unipolar (usually V_5). The 10-lead system allows monitoring of 12 leads simultaneously, the 3 standard limb leads (I, II, III), the 3 augmented limb leads (aVR, aVL, aVF), and 6 precordial leads (V_1 - V_6). The electrodes are placed on the right arm and leg, left arm and leg, and on the anterior and anterolateral chest wall. This allows for monitoring of specific areas of the heart. Leads V_1 to V_4 monitor the anterior wall; leads I, aVL, V_5 , and V_6 , the lateral wall; and II, III, and aVF, the inferior wall.

London and colleagues¹¹ examined lead sensitivity for detecting intraoperative myocardial ischemia. They concluded that using single-lead monitoring, V_5 had the greatest sensitivity, 75%, whereas V_4 had 61%. V_4 and V_5 combined had 90%. Sensitivity for the standard combination used in the clinical setting, II and V_5 , was 80%. Adding V_4 to II and V_5 increased the sensitivity to 96%. Although lead V_4 is more sensitive in detecting ischemia, lead II is superior in monitoring atrial arrhythmias.¹¹

Invasive ECG may monitor the cardiac electrical activity using leads placed in the trachea, the esophagus, in the cardiac cavities, or the coronary vessels but are not used in the routine anesthesia practice. The His bundle ECG uses an electrode on a catheter in the heart placed near the tricuspid valve (Figure 15.9). It records the activation of the AV node (A), the spreading of the electrical activity through the His bundle (H), and the ventricular depolarization (V). Information from the standard ECG and the His bundle ECG can be used to measure the time required for the impulse to travel between the sinus node and the AV node (AH) and through the AV node to the bundle of His and the ventricles. This allows detection of the site of a conduction delay, important for prognosis and treatment.

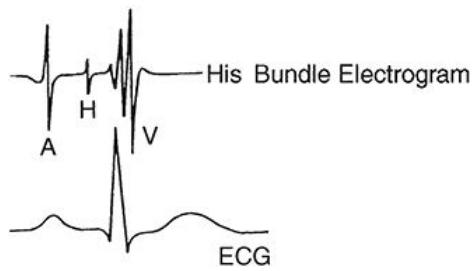


FIGURE 15.9 A normal His bundle electrogram and the corresponding electrocardiogram (ECG).

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Decreased voltage on the ECG may be caused by multiple small myocardial infarcts, which prevent generation of large quantities of electrical currents or abnormal conditions around the heart that impede current conduction from the heart to the skin, such as pericardial fluid and pulmonary emphysema.

It is important to differentiate artifacts from real ECG findings. Artifacts may be caused by malfunctioning ECG system (cables, connections, etc), improper skin preparation (oil, hair), lead misplacement/poor contact, patient's tremor/shivering, or muscular activity. External sources emitting electrical fields (electrocautery, 60-Hz power lines/light fixtures), cardiopulmonary bypass, somatosensory-evoked potential monitoring, and stimulators may also interfere with ECG recordings. All modern ECG monitors have incorporated filters for signal processing to minimize the presence of electrical artifacts.

Recording of the Electrocardiogram

The ECG is recorded digitally or on a graph paper consisting of 1-mm squares with every five squares separated by a darker line. Each 1-mm horizontal line represents 0.04 second, and each 1-mm vertical line represents 0.1 mV, assuming proper calibration 1 cm/1 mV and standardized paper speed of 25 mm per second. Therefore, the distance between two darker lines represents 0.2 second and 0.5 mV on the horizontal and the vertical axes, respectively. One minute (60 seconds) corresponds to 1,500 small or 300 big squares. The heart rate in beats per minute can be calculated by dividing 300 by the number of large boxes (or 1,500 by the number of small boxes) counted between two beats. Another method of calculating heart rate in beats per minute is to divide 60 by the number of seconds ($= 0.04 \text{ second} \times \text{number of small boxes}$) between two consecutive beats.

The electrical activity that activates the cardiac contraction is observed on a monitor display as a graph of voltage change through time. Modern monitors also have paper recorders allowing more thorough analysis of the ECG in complex situations. The Holter monitor is a small portable digital recorder that enables recording of the ECG for prolonged periods in ambulatory individuals to detect infrequent events.

Normal Electrocardiographic Deflections

Normally, the cardiac electrical impulse is initiated at the SA node, which is located at junction of the superior vena cava to the right atrium. Any part of the conduction system can spontaneously depolarize and initiate an impulse, but the SA node normally has the highest rate of depolarization and is the pacemaker of the heart. The impulse is transmitted through the right and left intra-atrial pathways to the AV node and then to the bundle of His and through the Purkinje fibers to the ventricular subendocardium, which causes the myocardium to depolarize from the endocardium to the epicardium. Repolarization happens in the reverse direction, from the epicardium to the endocardium. The speed of conduction is different between the various areas of the system, with the slowest through the AV node producing AV synchrony for optimal end diastolic filling from atrial contraction. The normal ECG consists of a P wave (atrial systole), a QRS complex (ventricular systole), and a T wave (ventricular repolarization). The atrial repolarization wave is obscured by the larger QRS complex ([Figure 15.10](#)).

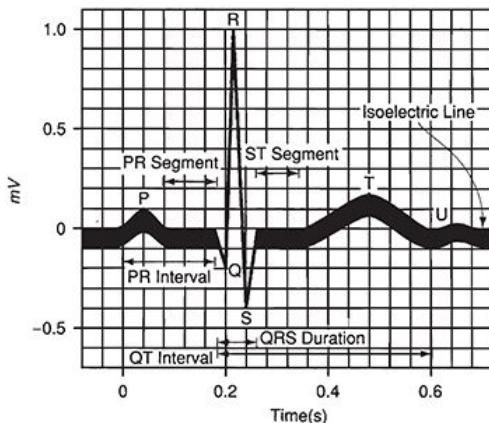


FIGURE 15.10 The normal waves and intervals on the electrocardiogram.

P Wave. The P wave represents the atrial depolarization and has a normal duration and amplitude of 0.08 to 0.12 second and less than 2.5 mm in the limb leads. Morphologically, it is positive in the standard limb leads and negative in aVR. Enlarged P wave signifies atrial enlargement.

P-R Interval. The P-R interval corresponds to the time from the beginning of the atrial depolarization to the beginning of the ventricular depolarization. It is measured from the start of the P wave to the start of the QRS and should not be confused with the PR segment, which is measured from the end of the P wave to the start of the QRS. The normal duration of the P-R interval is 0.12 to 0.2 second. Prolonged P-R interval is called first-degree AV block. In pericarditis, the P-R interval is depressed in most leads (whereas ST is elevated) and elevated in aVR (knuckle sign) ([Figure 15.11](#)).

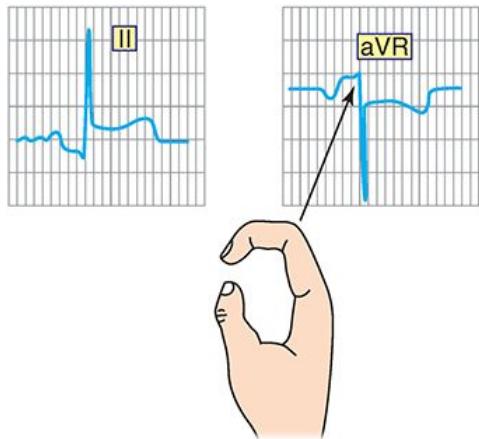


FIGURE 15.11 Acute pericarditis. Look for widespread ST segment elevation with concomitant PR depression in the same leads. The PR segment in aVR sticks above the baseline like a knuckle, reflecting atrial injury.

Q Wave. The Q wave is defined as an initial negative deflection of the QRS and is usually absent in leads aVR, V₁, and V₂. Normally, its duration is shorter than 0.04 second and its amplitude less than 0.4 to 0.5 mV. A Q wave whose amplitude is more than one-third of the corresponding R wave, duration is longer than 0.04 second, and depth is greater than 1 mm, is indicative of myocardial infarction (MI). The Q wave occurs because there is no electrical activity in the affected area. Therefore, the direction of the sum of the action potentials in the specific plane changes and is recorded accordingly. In the presence of anterior wall MI, Q

waves develop in leads V₂ to V₄; in anteroseptal MI, in leads V₁ to V₃; in anterolateral MI, in leads V₄ to V₆, I, and aVL; in lateral MI, in leads V₅, V₆, I, and aVL; and in inferior MI, in leads II, III, and aVF.

QRS Complex. The QRS complex is caused by the depolarization of the ventricles and normally has a duration of less than 0.10 second. A prolonged QRS duration may be due to left ventricular hypertrophy (LVH), impaired ventricular conduction (bundle branch block), beats initiated outside the conduction system (ectopic or paced beats), and beats passing through abnormal conduction pathways (Wolff-Parkinson-White syndrome). Normally, the QRS amplitude gradually increases in the precordial leads from V₁ to V₅, a phenomenon called **R wave progression**. The R wave is usually upright in the limb leads and downwardly deflected in aVR and V₁. Various criteria exist for defining LVH using the QRS amplitude. According to the Cornell criteria, LVH is present when the sum of the R wave in aVL and S wave in V₃ is greater than 28 mm in males and 20 mm in females. Based on the Sokolow-Lyon criteria, LVH is present when the S wave in V₁ + (R in V₅ or R in V₆) is greater than 35 mm or R in aVL is greater than 11 mm.

ST Segment. The ST segment starts when all myocardial cells are depolarized (end of QRS) and ends when ventricular repolarization begins (T wave). It is normally isoelectric, and elevation or depression more than 1 mm from the baseline may indicate myocardial ischemia. Hyperkalemia and pericarditis may also cause ST elevation. J point elevation (where QRS and ST segment connect) and normal variants of early repolarization are nonpathologic findings that must be excluded ([Figure 15.12](#)).

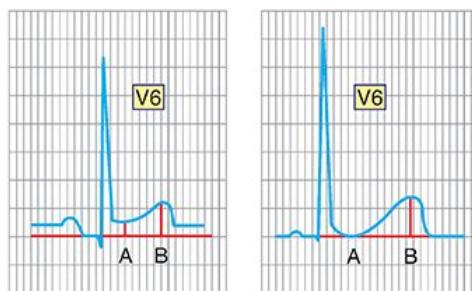


FIGURE 15.12 Differentiating pericarditis from early repolarization. Only lead V₆ is used. If A/B is greater than 25%, suspect pericarditis. If A/B is less than 25%, suspect early repolarization.

T Wave. The T wave is caused by the repolarization of the ventricles, and its normal amplitude is less than 10 mm in the precordial leads and 6 mm in the limb leads. Usually, in any lead, the T wave is deflected in the same directions as the QRS. Delay of conduction of cardiac impulses through the ventricles (prolonged depolarization), as occurs with myocardial ischemia, bundle branch blocks, or ectopic ventricular beats, may result in T-wave polarity opposite the QRS complex. Symmetrical or deeply inverted T waves may be indicative of myocardial ischemia. Inverted T waves in V₁ to V₃ in children (juvenile T waves) and occasionally in women can be a normal variant. Peaked T waves may be present in hyperkalemia, LVH, and intracranial bleeding.

U Wave. The U wave, when present, follows the T wave, and it probably represents part of the ventricular repolarization. It is most prominent in V₂ and V₃. Causes of increased U wave amplitude (>1.5 mm) include LVH, bradycardia, ischemia, electrolyte abnormalities (low potassium, magnesium, calcium), and medications.

QT Interval. The QT interval includes both ventricular depolarization and repolarization. It is measured from the beginning of the QRS to the end of the T wave and varies in duration according to heart rate. The QT interval corrected for heart rate (QTc) is calculated by dividing the QT interval by the squared root of the R-R interval. Prolonged QTc (>0.44 second) may be associated with ventricular arrhythmias. Causes of prolonged

QT include hypocalcemia, hypomagnesemia, medications, severe bradycardia, hypothermia, ischemia, intracranial hemorrhage, and myxedema of hypothyroidism.

Cardiac Physiology

Myocardium

The myocardium is the involuntary, striated muscle tissue in the heart between the epicardium and the endocardium; its cells are called **cardiomyocytes**. The primary structural proteins of the cardiac muscle are actin and myosin filaments, which interdigitate and slide along each other during contraction in a manner similar to skeletal muscle. But unlike the skeletal muscle in which the actin and myosin filaments are linear and longitudinal, in cardiomyocytes, they are branched ([Figure 15.13](#)).¹² Also, the cardiac T tubules are larger and broader and fewer in number than skeletal muscle. Cardiac muscle T tubules form dyads with the sarcoplasmic reticulum intercalated discs with permeable junctions that allow rapid diffusion of ions so that action potentials travel easily from cell to cell. Thus, cardiomyocytes are functionally interconnected in a syncytium so that activation of one cell results in the spread to all connected cells. The atrial syncytium is separated from the ventricular syncytium by the fibrous tissues around the AV valves, and the cardiac action potential is normally only conducted from the atria to the ventricles by a specialized conduction pathway through the AV node.¹³



FIGURE 15.13 “Syncytial” interconnecting nature of cardiac muscle fibers.¹² Reprinted from Hall JE. Guyton and Hall Textbook of Medical Physiology. 12th ed. Philadelphia, PA: Saunders/Elsevier; 2011. Copyright © 2011 Elsevier. With permission.

Cardiac Action Potential

At the initiation of an action potential in a cardiomyocyte, the cell membrane rapidly depolarizes as the transmembrane potential rises from -85 mV to $+20\text{ mV}$. The membrane remains depolarized for about 0.2 second, the plateau phase, which is then followed by rapid repolarization. This plateau causes the contraction of a cardiomyocyte to last much longer than a skeletal muscle cell and is due to the slow calcium channels, which open after the sodium channels and remain open several tenths of a second. Depolarization of the cardiomyocyte is also prolonged by a decrease in permeability of the potassium channels after initiation of the action potential, another difference from skeletal muscle. During the plateau phase, the cardiomyocyte cannot be restimulated for about 0.25 to 0.3 second, called the **refractory period**. This is followed for additional 0.05 second by the relative refractory period, when the myocardium can only be stimulated by a strong excitatory signal.^{12,14}

Excitation-Contraction Coupling

Excitation-contraction coupling in both cardiac and skeletal muscle occurs when the action potential spreads into the cell through transverse tubules (T tubules). Depolarization of the T tubule causes influx of calcium into the sarcoplasm, which binds to troponin activating the contraction of actin and myosin filaments. In the

cardiomyocyte, however, the initial influx of calcium ions is just a small fraction of the amount needed for contraction, and it triggers an additional release of calcium from the sarcoplasmic reticulum into the sarcoplasm. The structural differences between cardiac and skeletal muscle reflect the difference in coupling mechanism. Myocardium has sparser and less developed sarcoplasmic reticulum, and the T tubules are larger and store more calcium.^{15,16}

Control of Cardiac Function

Neural Control

Heart function is controlled by the autonomic nervous system by both adrenergic and muscarinic acetylcholine receptors, modulating the cardiac output (CO) by influencing heart rate and myocardial contraction. The sympathetic nervous system, through adrenergic receptors with the neurotransmitter norepinephrine, has positive inotropic, chronotropic, and lusitropic effects on the heart. The parasympathetic nervous system, acting through muscarinic receptors with the neurotransmitter acetylcholine, has a more direct inhibitory effect on the heart through the vagal nerve, reducing heart rate, AV node conduction, and cardiac contractility. The atria are innervated by both the sympathetic and parasympathetic nervous system, but the ventricles are supplied principally by the sympathetic nervous system (**Figure 15.14**).^{12,17}

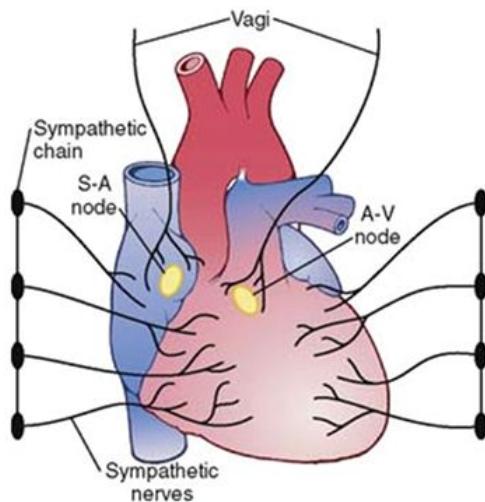


FIGURE 15.14 Cardiac sympathetic and parasympathetic nerves.¹² Abbreviations: A-V, atrioventricular; S-A, sinoatrial. Reprinted from Hall JE. Guyton and Hall Textbook of Medical Physiology. 12th ed. Philadelphia, PA: Saunders/Elsevier; 2011. Copyright © 2011 Elsevier. With permission.

Sympathetic nervous system fibers to the heart continually discharge at a slow rate maintaining a strength of ventricular contraction about 20% to 25% above the unstimulated state. Maximal sympathetic nervous system stimulation can increase CO by about 100% above normal. Conversely, maximal parasympathetic nervous system stimulation decreases ventricular contractile strength only by about 30%, as the vagal innervation is sparse in the ventricles. Strong stimulation of the parasympathetic system can result in a period of asystole, followed by an escape rhythm between 20 and 40 beats per minute.^{12,18}

Hormonal Control

Many hormones can have direct and indirect action on the heart during normal or pathophysiologic conditions. These hormones are produced within cardiomyocytes or by other tissues in the body. The hormones secreted by cardiomyocytes include natriuretic peptide, adrenomedullin, aldosterone, and angiotensin II.^{19–21} Atrial (ANP) and B-type (BNP) natriuretic peptides are released from atria and ventricle in response to increased stretch of the chamber wall. Both ANP and BNP participate in homeostasis of body fluids, in regulation of blood pressure, and in growth and development of cardiac tissue. In chronic heart failure, high ANP and BNP levels have been associated with increased mortality.¹⁹ Adrenomedullin is a

peptide hormone that increases level of cyclic adenosine monophosphate and has positive inotropic and chronotropic effects on the heart and is a vasodilator. The renin-angiotensin system is an important regulator of the cardiovascular system. Angiotensin II stimulates AT₁ receptors with positive inotropic and chronotropic effects. Synthetic angiotensin II has been shown to effectively increase blood pressure in patients with catecholamine resistant shock.²² However, the FDA warns administration may be associated with increased thrombosis risk.²³

It also mediates cell growth and proliferation of cardiomyocytes, thus playing an important role in development of remodeling during cardiac hypertrophy and heart failure.²¹

Cardiac Cycle

Electrical and Mechanical Events

The cardiac cycle is a series of coordinated electromechanical events that result in the ejection of blood from the heart into the great vessels. Ventricular systole is defined as the period of myocardial contraction when the aortic and pulmonic valves are open and diastole as the period of relaxation and ventricular filling when the mitral and tricuspid valves are open. Each mechanical event is preceded by an electrical depolarization that generates an action potential and subsequent contraction.

Wiggers²⁴ elegantly illustrated the mechanical, electrical, and acoustic events of the cardiac cycle. His diagram depicts the aortic, ventricular, and atrial pressure tracings with concomitant ECG, ventricular volume, and auscultatory findings (**Figure 15.15**).²⁴ Systole begins with isometric contraction (A-C), followed by opening of the aortic valve and ejection of blood into the aorta, with a period of maximum ejection (C-D) and reduced ejection (D-F). Isometric contraction starts with closure of the mitral valve and ends with opening of the aortic valve, during which time no volume enters or leaves the ventricle. Approximately two-thirds of stroke volume (SV) is ejected during the period of maximum ejection and one-third during the period of reduced ejection. The ventricular volume curve that coincides with this event is inversely related to the aortic and ventricular pressure curves. Simultaneous electrical depolarization corresponds with the QRS complex of the ECG.

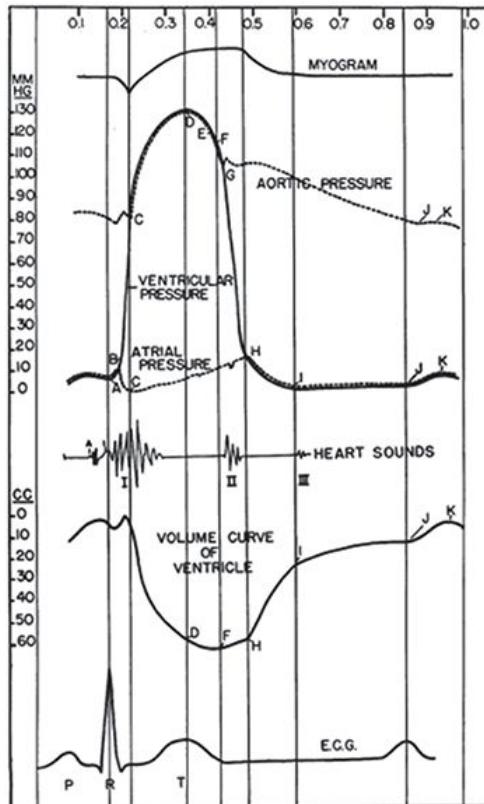


FIGURE 15.15 Cardiac cycle: mechanical, electrical, and acoustic events. Reprinted with permission from Wiggers CJ. Dynamics of ventricular contraction under abnormal conditions. Circulation. 1952;5(3):321-348. Copyright © 1952 American Heart Association, Inc.

Diastole follows systole and is divided into prodiastole (F and G), isometric relaxation (G and H), rapid ventricular filling (H and I), diastasis (I and J), and filling by atrial contraction (J and K). During prodiastole, the semilunar, aortic, and pulmonic valves close. This is followed by isometric relaxation, the time between closure of the aortic valve and opening of the mitral valve. Ventricular filling depends on both the relaxation of the myocardium and chamber compliance.²⁵ There is a period of diastasis with minimal flow during which the ventricular volume remains relatively constant. This is followed by atrial contraction during late diastole, synchronous with the P wave of atrial depolarization on the ECG.

The atrial pressure tracing, or central venous waveform, begins with an “a” wave that corresponds to atrial contraction at end diastole. The “c” wave represents ventricular systole during which time the right atrial pressure increases slightly as the right ventricle contracts against a closed tricuspid valve. The subsequent downward slope in the waveform, the “x descent,” corresponds to atrial relaxation. The “v” wave occurs during venous filling of the right atria toward the end of systole. The “y descent” represents a fall in right atrial pressures as the tricuspid valve opens and the right ventricle fills in diastole ([Figure 15.16](#)).²⁶



FIGURE 15.16 Central venous waveform. Reprinted with permission from Pittman J, Ping JS, Mark JB. Arterial and central venous pressure monitoring. Int Anesthesiol Clin. 2004;42(1):13-30.

Myocardial Performance, Preload, and Afterload

In the early 1900s, Frank Otto and Ernest Henry Starling described what is known today as the Frank-Starling mechanism. In a series of publications, they demonstrated that myocardial stretch, called **preload**, induced by increased venous return to the heart augments cardiac output²⁷ and that increased end diastolic volume (EDV) or right atrial pressure enhances myocardial contractility.^{28,29}

In canine experiments, Arthur C. Guyton³⁰ identified two factors affecting venous return or preload to the ventricle: right atrial pressure and mean circulatory filling pressure. Higher right atrial pressure diminishes venous return to the heart, whereas higher mean circulatory filling pressure, as measured by temporary cessation of CO and equilibration of peripheral pressures, increases venous return. Increasing mean circulatory filling pressure, for example, by transfusion, enhances venous return to the heart, thereby augmenting CO without affecting contractility. He synthesized these findings with the Frank-Starling mechanism and graphically displayed superimposing cardiac response and venous return curves ([Figure 15.17](#)).^{30,31}

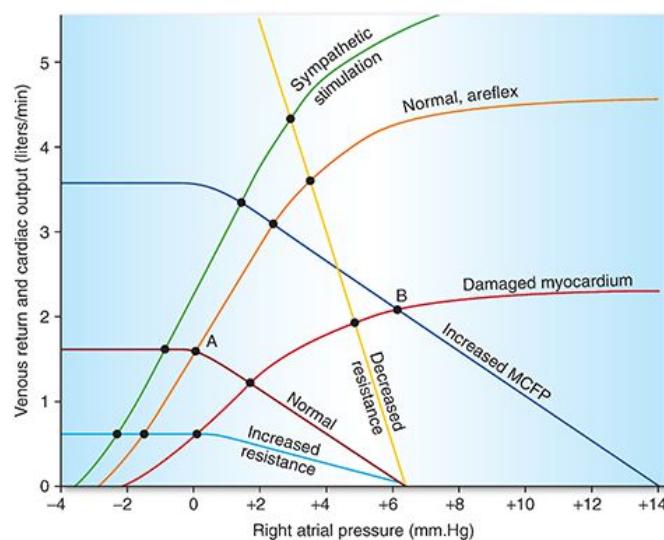


FIGURE 15.17 Determinants of cardiac output. MCFP, mean circulatory filling pressure. Reprinted with permission from Guyton AC. Determination of cardiac output by equating venous return curves with cardiac response curves. Physiol Rev. 1955;35(1):123-129. Copyright © 1955 the American Physiological Society.

Afterload refers to the resistance or pressure against which the ventricle contracts. Mechanical obstruction such as aortic stenosis increases afterload and adversely affects myocardial performance. Pharmacologic interventions such as the administration of phenylephrine can increase afterload as well by increasing systemic vascular resistance (SVR). Afterload in its simplest interpretation often refers to the mean arterial pressure (MAP).

The LV pressure-volume loops can be used to demonstrate how changes in preload and afterload affect SV and end systolic and end diastolic pressure-volume relationships. The entire loop represents a single cardiac cycle with volume on the x-axis and pressure on the y-axis. The difference between EDV and end systolic volume (ESV) equals SV. At end diastole, after closure of the mitral valve, isometric contraction increases the pressure in the LV cavity marking the beginning of systole. When the LV pressure exceeds that in the aorta, the aortic valve opens and ejection begins. After end systole and peak LV pressure, the aortic valve closes. This is followed by a brief period of isometric relaxation marking the beginning of diastole during which LV pressure falls and the LV volume does not change. Then the mitral valve opens, the LV fills accommodating the SV to be ejected during the subsequent cardiac contraction ([Figure 15.18A](#)).

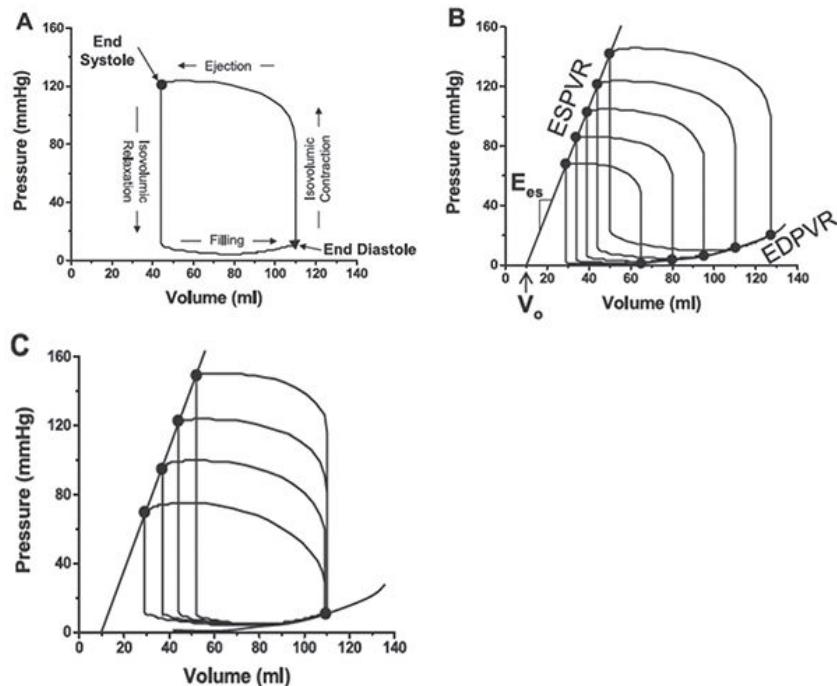


FIGURE 15.18 A, Pressure-volume loop of a single cardiac cycle. B, A reduction in ventricular filling pressure causes the loops to shift toward lower end systolic and end diastolic function. C, When afterload is increased, the loops get narrower and longer. Abbreviations: EDPVR, end diastolic pressure-volume relationship; E_{es} , slope of linear ESPVR; ESPVR, end systolic pressure-volume relationship; V_o , volume axis intercept. Reprinted with permission from Burkhoff D, Mirsky I, Suga H. Assessment of systolic and diastolic ventricular properties via pressure-volume analysis: a guide for clinical, translational, and basic researchers. Am J Physiol Heart Circ Physiol. 2005;289(2):H501-H512. Copyright © 2005 by the American Physiological Society.

A drop in preload, for example, with clamping of the inferior vena cava, will decrease SV, ESV, and EDV. The shape of the pressure-volume loop narrows, shortens, and shifts to the left ([Figure 15.18B](#)).³² An increase in afterload, for example, with administration of phenylephrine, will cause end systolic pressure and volume to increase and SV to decrease, the loops get narrower and longer ([Figure 15.19C](#)).³² The slope of the end systolic pressure-volume relationship is referred to as **elastance** and labeled “ E_{es} ” in the figures. It

stays constant during changes in preload and afterload, is a measure of the strength of contraction, or contractility, and is steeper with increased contractility.^{33,34}

Hemodynamic Calculations

The CO is equal to heart rate multiplied by SV. As illustrated in the previous LV pressure-volume loops, $SV = EDV - ESV$. Mean arterial pressure (MAP) is two-thirds diastolic blood pressure plus one-third systolic blood pressure. The MAP is also CO multiplied by SVR (**Table 15.2**).

TABLE 15.2

Hemodynamic equations

$$CO = HR \times SV$$

$$CI = CO / BSA$$

$$SV = EDV - ESV$$

$$MAP = CO \times SVR$$

$$MAP = 2/3 \text{ diastolic pressure} + 1/3 \text{ systolic pressure}$$

$$SVR = [(MAP - CVP) / CO] \times 80$$

$$PVR = [(mean PAP - wedge) / CO] \times 80$$

Abbreviations: BSA, body surface area; CI, cardiac index; CO, cardiac output; CVP, central venous pressure; EDV, end diastolic volume; ESV, end systolic volume; HR, heart rate; MAP, mean arterial pressure; PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance; SV, stroke volume; SVR, systemic vascular resistance.

There are several methods to measure CO, the volume of blood delivered by the heart to the body per minute, including thermodilution, the Fick method, and echocardiography. The thermodilution method uses a pulmonary artery (Swan-Ganz) catheter through which cool saline is injected into the right atrium. The cool saline mixes with warmer blood, and the temperature change is recorded by a thermistor at the tip of the catheter, positioned in the main pulmonary artery. The CO is inversely proportional to the integral of the time-temperature curve.^{35,36} Limitations of this method include tricuspid regurgitation and the presence of intracardiac shunts. Tricuspid regurgitation will underestimate the CO, as the cool injectate travels retrograde into the vena cava increasing the time it takes to reach the pulmonary artery. Conversely, intracardiac left to right shunts can falsely overestimate the CO.

The CO can also be measured using the Fick method. Fick CO (liters per minute) = (oxygen consumption VO_2) / [(arteriovenous oxygen difference) $\times 10$] Oxygen consumption can be estimated based on a nomogram that accounts for patient age, sex, height, and weight. It can also be directly measured by exhaled breath analysis. The value 250 mL oxygen per minute is often used as a standardized reference. The difference in arterial versus venous oxygen content ($Cao_2 - Cvo_2$) is calculated by the following formula:

$$(Cao_2 - Cvo_2) = (1.34 \times Hgb \times SaO_2) - (1.34 \times Hgb \times Svo_2)$$

where SaO_2 is the arterial oxygen saturation and Svo_2 is the mixed venous oxygen saturation, that is, the saturation of pulmonary arterial blood. The arterial venous oxygen difference is inversely related to CO as long as the oxygen consumption of the body is constant.

Lastly, CO can be calculated by echocardiography. Pulsed wave Doppler is used to record the velocity profile of flow in the LVOT. Tracing this profile gives the velocity time integral (VTI) in centimeters. The LVOT VTI is multiplied by area of the LVOT in square centimeters to obtain the SV in milliliters. The LVOT is assumed to be circular in shape. The area of a circle is πr^2 . The diameter of the LVOT is measured with two-dimensional echocardiography and divided by two to obtain the radius in the area calculation. Therefore, $SV = LVOT VTI \times LVOT \text{ area } (\pi r^2)$. A similar calculation can be made to obtain the SV through the right ventricular outflow tract. The two numbers are identical provided there is no intracardiac shunt or regurgitation of the aortic or pulmonic valves. Multiplying the SV by the patient's heart rate yields CO.

After obtaining CO by one of these three methods, one can calculate SVR and pulmonary vascular resistance. The SVR in Wood units is the MAP less the central venous pressure divided by CO (see [Table 15.2](#)). To convert from Woods units to dynes/s/cm⁵, the result is multiplied by 80. Similarly, to calculate pulmonary vascular resistance, the pulmonary artery occlusion pressure (a surrogate for the left atrial pressure) is subtracted from the mean pulmonary arterial pressure, and the result is divided by CO. The same conversion from Woods units applies. Obtaining CO and calculating SVR can often aid in narrowing a differential diagnosis in various types of shock. An Svo₂ can also assist in narrowing the differential. Together, this information can guide therapeutic intervention toward inotropic support, volume administration, titration of vasopressors, or consideration of mechanical assist devices. In cardiogenic shock, for example, CO will be low, SVR high, and mixed venous saturation low. This is in contrast to vasodilatory or septic shock in which CO will be high, SVR low, and mixed venous saturation usually high. Normal hemodynamic values are listed in [Table 15.3](#).

TABLE 15.3

Normal hemodynamic values

Cardiac index = 2.4 L per minute

Cardiac output = 5-7 L per minute

Stroke volume = 70-90 mL (1 mL/kg)

MAP = 60-90 mm Hg

CVP = 5-10 mm Hg

SVR = 800-1,200 dyne/s/cm⁵

PVR = <250 dyne/s/cm⁵

PAOP = 6-12 mm Hg

Mean PAP = 10–20 mm Hg

Abbreviations: CVP, central venous pressure; MAP, mean arterial pressure; PAOP, pulmonary artery occlusion pressure; PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance.

Pathophysiology

Ischemic Heart Disease

Ischemic heart disease refers to atherosclerosis of the coronary arteries that obstructs blood flow to the myocardium resulting in either stable symptoms, which can be medically managed, or unstable acute coronary syndromes (ACS), which may call for more invasive intervention such as revascularization by percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery. The development of atherosclerosis is an inflammatory process mediated by adherent leukocytes (phagocytes and T lymphocytes), cytokines, and smooth muscle cells that generate a lipid-rich necrotic plaque.³⁷⁻³⁹ Coronary microvascular disease is an important consideration in patients with a nonobstructive cardiac catheterization, who may also be at risk for major adverse cardiac events.⁴⁰ Risk factors for ischemic heart disease include diabetes, renal impairment, hypertension, cigarette smoking, hyperlipidemia, and abdominal obesity.

The ACS are categorized as non-ST elevation ACS (including unstable angina) or ST elevation MI (STEMI). All suspected patients are evaluated with a 12-lead ECG and troponin. For patients with possible ACS and negative workup, coronary CT angiography is recommended (class IIa).⁴¹

Those with suspected non-ST elevation ACS are managed with dual antiplatelet therapy (DAPT), anticoagulation, and either an ischemia-guided strategy (initial noninvasive evaluation for low risk patients) or early invasive strategies. Invasive strategy includes evaluation with diagnostic angiography for consideration of PCI or coronary artery bypass graft. Timing depends on patient stability and symptoms and classified as immediate (<2 hours), early (within 24 hours), or delayed (25-72 hours).^{41,42}

Medical management of stable ischemic heart disease begins with risk factor reduction. β Blockade has been shown to confer a survival benefit in patients with prior MI or a low ejection fraction and decreases myocardial oxygen consumption. Oral or sublingual nitrates are effective in angina prophylaxis or during acute episodes. Antiplatelet agents such as aspirin are indicated unless bleeding precludes their use.⁴³⁻⁴⁵ A DAPT is indicated for patients who have received a PCI. The duration of DAPT depends on the indication for PCI and type of stent, either bare metal or drug eluting. For those patients receiving a drug-eluting stent after an MI, DAPT is indicated for a year.^{46,47} Longer duration of DAPT can be considered by calculating a DAPT score.⁴⁸ Both prasugrel and ticagrelor have been shown to be superior to clopidogrel after MI when combined with aspirin.^{49,50} In a recent study, prasugrel was shown to be superior to ticagrelor in ACS with a lower incidence of death, MI, and stroke. Both groups had similar rates of bleeding.⁵¹ Guidelines will continue to evolve based on this literature. Statins are indicated for their lipid-lowering effects and antiinflammatory properties. Angiotensin-converting enzyme inhibitors assist in ventricular remodeling after MI and are class I indicated in patients with chronic kidney disease or LV ejection fraction <40%, hypertension, or diabetes mellitus.⁴¹ Diuretics optimize volume status and provide symptom relief in patients with heart failure.

Heart Failure

Heart failure is defined as “a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood.”⁵²⁻⁵³ The underlying etiologies are numerous and include ischemia, hypertension, and diabetes. Other less common causes are valvular heart disease, infections such as viral myocarditis, toxins (alcohol, chemotherapeutic agents), and obesity.^{54,55}

The American College of Cardiology/American Heart Association and the New York Heart Association functional classifications describe heart failure according to symptoms (**Table 15.4**). Heart failure can also be classified by ventricular function or ejection fraction. Heart failure with preserved ejection fraction, or diastolic heart failure, comprises those patients with an ejection fraction greater than 50% with echocardiographic evidence of abnormal diastolic function, an impairment in relaxation, and ventricular filling. The most important risk factor for diastolic heart failure is hypertension. Diastolic heart failure is more common in the elderly, female, and obese populations^{55,56} and has now surpassed systolic heart failure as the leading class of heart failure.⁵⁷ Hospitalizations for heart failure with preserved ejection fraction are increasing over time, with minimal advancement in treatment modalities.⁵⁸ Risk factor modification including treatment of underlying hypertension is imperative.

TABLE 15.4

ACCF/AHA stages of HF and NYHA functional classification

ACCF/AHA stages of HF	NYHA functional classification	
A At high risk for HF but without structural heart disease or symptoms of HF		None
B Structural heart disease but without signs or symptoms of HF	I	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.
C Structural heart disease with prior or current symptoms of HF	I II III	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF. Slight limitation of physical activity. Comfortable at rest but ordinary physical activity results in symptoms of HF. Marked limitation of physical activity. Comfortable at rest but less than ordinary activity causes symptoms of HF.
D Refractory HF requiring specialized interventions	IV	Unable to carry on any physical activity without symptoms of HF or symptoms of HF at rest
	IV	Unable to carry on any physical activity without symptoms of HF or symptoms of HF at rest

Abbreviations: ACCF, American College of Cardiology Foundation; AHA, American Heart Association; HF, heart failure; NYHA, New York Heart Association.

Reprinted from Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;62(16):e147-e239. Copyright © 2013 American College of Cardiology Foundation and the American Heart Association, Inc. With permission.

Heart failure with reduced ejection fraction occurs in patients with an ejection fraction less than 40%. Patients often have concomitant diastolic dysfunction. One of the main risk factors for heart failure with reduced ejection fraction is coronary artery disease. Treatment modalities range from oral medication to intravenous inotropes to mechanical assist devices. Diuretics, angiotensin-converting enzyme inhibitors, and β -blockers have been the foundation of medical management. Digoxin provides symptom relief and decreases hospital admissions, although it has no mortality benefit.⁵⁹ It can be useful in patients with associated atrial fibrillation to control heart rate. Patients with decompensated systolic heart failure may require acute positive inotropic therapy with milrinone, dobutamine, or epinephrine. More invasive methods to support the failing ventricle include intra-aortic balloon counterpulsation, ventricular assist devices, and cardiac transplantation.^{60,61} New ventricular assist device technology is rapidly evolving, and the use of a fully magnetically levitated LV assist device, a centrifugal pump, known as the HeartMate 3 (Abbott, Santa Clara, CA), has been shown to have a decreased incidence of stroke and reoperation for device thrombosis compared to the earlier generation axial flow HeartMate II (Abbott, Santa Clara, CA) LV assist device.^{62,63} Both hemorrhagic and ischemic strokes, either disabling or nondisabling, have been associated with markedly reduced long-term survival with LV assist device therapy.⁶⁴

Valvular Heart Disease

Aortic Stenosis

Aortic stenosis is the most common valvular heart disease in elderly patients. It occurs as the trileaflet aortic valve calcifies with age, with congenitally bicuspid aortic valves in a younger patient population, or secondary to rheumatic heart disease. Symptoms usually develop when the valve area is less than 1 cm^2 , considered within the severely stenotic range. The typical presentation is either chest pain, syncope, or dyspnea (ie, heart failure) at which time patients are estimated to have a 5-, 3-, or 2-year 50% mortality, respectively.⁶⁵ Other conditions that may resemble aortic stenosis include hypertrophic cardiomyopathy, supravalvular stenosis, or subaortic membrane. The ventricle usually hypertrophies as a compensatory response to the increased afterload of the stenotic orifice, and diastolic dysfunction is a common finding. Even with normal coronary arteries, patients are at risk for subendocardial ischemia due to the severity of LVH. Hemodynamic optimization of these patients, especially during induction of anesthesia, includes maintaining adequate preload, a higher MAP, and lower heart rate. This allows more time for ventricular filling in the noncompliant heart while maintaining acceptable systemic perfusion to compensate for the increased transvalvular pressure gradient and relatively fixed CO.

Aortic Insufficiency

Aortic insufficiency can develop acutely or be more chronic in nature. Acute aortic insufficiency can be a result of trauma, endocarditis, or dissection. The pathophysiology of the two entities differs given that with chronic regurgitation, the ventricle has time to compensate by dilating and increasing diastolic compliance. This does not occur if the regurgitation occurs acutely. Aortic regurgitation in type A aortic dissection can be due to annular and aortic root dilation, asymmetric cusp coaptation due to pressure from a false lumen, flail aortic cusp due to annular disruption, or prolapse of the intimal flap through the valve ([Figure 15.19](#)).⁶⁶ Acute, severe aortic insufficiency results in severe elevation in LV end diastolic pressure and can cause presystolic closure of mitral valve during diastole, diastolic mitral regurgitation, acute pulmonary edema, and heart failure.⁶⁶

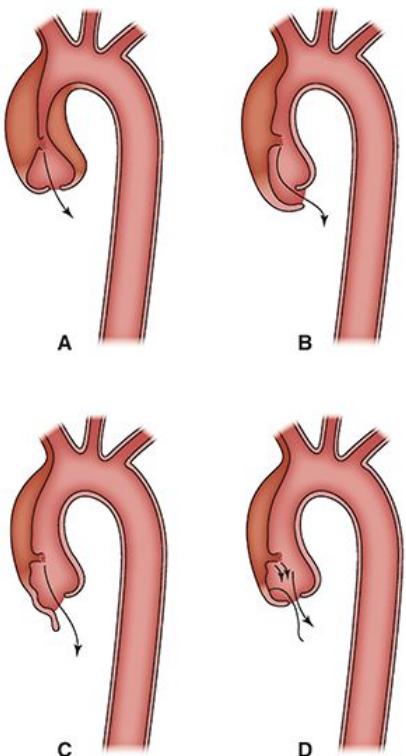


FIGURE 15.19 A-D, Mechanism of aortic regurgitation in proximal aortic dissection. Reprinted from Isselbacher EM, Eagle KA, Desanctis RW. Diseases of the aorta. In: Braunwald E, ed. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. Vol 2. 5th ed. Philadelphia, PA: Saunders Co.; 1997:1557. Figure 45-8. Copyright © 1997 Elsevier. With permission.

Chronic aortic insufficiency is characterized by volume and pressure overload of the left ventricle. Class I indications for surgery for severe aortic insufficiency include an ejection fraction of less than 50%, symptoms related to aortic insufficiency, and patients undergoing cardiac surgery for another reason.^{67,68} Patients with chronic aortic insufficiency often have a dilated LV cavity as a result of volume overload, and surgery is a reasonable consideration in asymptomatic patients with an LV end diastolic dimension of greater than 65 mm or an LV end systolic dimension of greater than 50 mm (class II recommendation).⁶⁸

Mitral Stenosis

Mitral stenosis is most often due to rheumatic heart disease, although it can be congenital or degenerative as well. With rheumatic mitral stenosis, thickening and fusion of the mitral commissures and leaflets and chordal thickening leads to a restricted orifice. Symptoms related to mitral stenosis are secondary to volume and pressure overload of the pulmonary circulation due to a fixed obstruction to LV filling. The LV end diastolic and ESVs are lower compared to a normal heart due to the left atrial-LV pressure gradient. Hemodynamic goals include avoiding tachycardia, which further decreases diastolic filling time. Any factors that further increase pulmonary hypertension should be avoided.

Mitral Regurgitation

Etiologies of mitral valve regurgitation include degenerative disorders; rheumatic disorders; congenital disorders; and disorders related to coronary artery disease, endocarditis, or trauma. Characterizing the mechanism of mitral regurgitation, when severe, helps decide whether repair or replacement is feasible.⁶⁹ Mitral regurgitation can be a result of annular dilation, excessive leaflet motion (prolapse or flail), or restricted leaflet motion. The Carpentier classification describes the mechanisms of various types of mitral regurgitation.⁷⁰ Carpentier class I refers to functional mitral regurgitation related to a dilated annulus, class II

refers to excessive leaflet motion in which the regurgitant jet is directed away from the degenerative leaflet, and class III refers to restricted leaflet motion in which the regurgitant jet is ipsilateral to the effected leaflet or central in the case of bileaflet restriction ([Figure 15.20](#)). Class IIIa is restricted leaflet motion involving the subvalvular apparatus (chordae and papillary muscles) seen in rheumatic heart disease. Class IIIb is restricted leaflet motion that often accompanies ischemic heart disease, in which the subvalvular apparatus is unaffected, although ventricular wall motion may be compromised. Traditionally, mitral repair with preservation of the chordal apparatus has been favored over replacement, with evidence of decreased mortality and improvement of ejection fraction, although some more recent studies have suggested otherwise.[71–74](#)

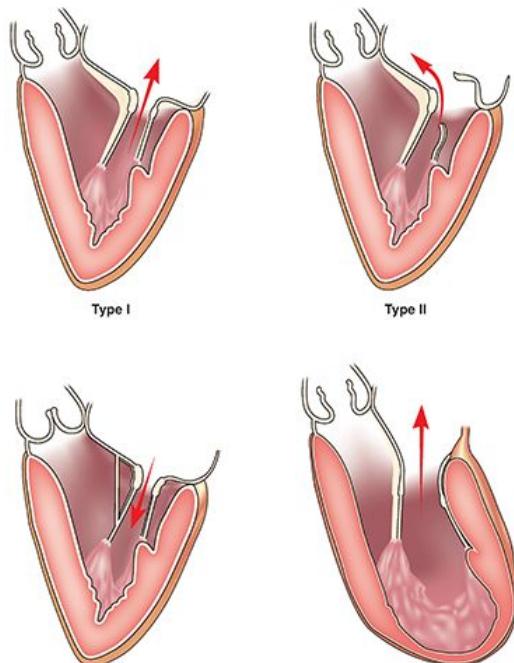


FIGURE 15.20 Carpentier classification of patients with mitral regurgitation (MR). Type I MR: normal leaflet length and motion but with annular dilation or leaflet perforation; type II MR: caused by leaflet prolapse, usually from myxomatous disease, papillary muscle rupture, or elongation; type IIIa MR: rheumatic disease with subvalvular involvement; type IIIb MR: caused by ischemic or idiopathic cardiomyopathy causing tethering or restriction of leaflets. Republished with permission of McGraw Hill LLC from Filsoufi F, Adams DH. *Surgical treatment of mitral valve endocarditis*. In: Cohn LH, Edmunds LH Jr, eds. *Cardiac Surgery in the Adult*. 2nd ed. New York, NY: McGraw-Hill, 2003:987-997; permission conveyed through Copyright Clearance Center, Inc.

Indications for surgical intervention in valvular heart disease include the following considerations: the presence of symptoms, the severity of the valvular lesion, the response of the ventricles to the volume and pressure overload, the effects of this overload on the pulmonary and systemic circulations, and the development of arrhythmias related to the lesions.[68](#) Patient comorbidities may make percutaneous procedures more favorable. The development and the transcatheter aortic valve implantation procedures, for example, offer an alternative to open heart surgery in those patients with severe aortic stenosis who are high-, intermediate-, and low-risk surgical candidates with improved survival and decreased risk of stroke.[75](#) Patients with endocarditis or bicuspid valves were excluded from these trials.[76–81](#)

Cardiac Dysrhythmias

During the perioperative period, changes may take place that trigger cardiac dysrhythmias. It is important to monitor for arrhythmias throughout this time, as they may cause hemodynamic instability and increase

morbidity and mortality. The incidence varies according to the type of surgery, morphology of arrhythmia, the form of monitoring (continuous vs intermittent), and the patient's history. A multicenter study with 17,201 patients undergoing a variety of procedures concluded that 70.2% had dysrhythmias (bradycardia, tachycardia, other arrhythmias) and 1.6% of these needed treatment.⁸² Bertrand et al⁸³ reported an incidence of 84% and noted that arrhythmias presented more often during the endotracheal intubation and extubation phases. Atlee⁸⁴ reported in patients undergoing cardiothoracic surgery, the incidence of some arrhythmia may exceed 90% with continuous monitoring. Melduni et al⁸⁵ reported it ranges from 4% to 20% for noncardiothoracic surgeries.

Etiology

Perioperative cardiac dysrhythmias are most likely to occur in patients with preexisting heart disease (coronary artery disease, valvular heart disease, or cardiomyopathies). Transient physiologic imbalances during the perioperative period make the heart more susceptible to abnormalities in the automaticity of pacemaker cells, the excitability of myocardial cells, and the conduction of the cardiac impulse.

Factors that may contribute to such imbalances include the following:

- Laryngoscopy, endotracheal intubation, ischemia, and release of catecholamines
- Electrolyte abnormalities, hypoxia, carbon dioxide levels, and pH changes
- Inhalation anesthetics, succinylcholine, anticholinesterase-anticholinergic combination reversal, most serotonin type 3 antagonists, droperidol, domperidone, and antiarrhythmics may prolong the QT interval and trigger arrhythmias.
- Extensive blockade of the sympathetic system by subarachnoid local anesthetics may produce bradyarrhythmias and prolong the QT interval.⁸⁶
- Ketamine due to its cardiovascular-stimulating properties
- Direct stimulation of the heart during cardiothoracic procedures and catheter insertion or stimulation of the autonomic nervous system (vagal response)

Mechanisms of Arrhythmia

Automaticity

Automaticity of the heart is its ability to spontaneously generate an electrical impulse to initiate contraction. Any cell of the cardiac conduction system can trigger its own action potential and act as a pacemaker, including cells in the SA node, the AV node, and specialized conducting fibers of the atria and ventricles. Normally, the highest rate of spontaneous depolarization occurs in the SA node, making it the dominant pacemaker in the heart. Abnormal automaticity of any part of the conduction system can lead to arrhythmias.

The resting membrane potential of the pacemaker cells is -60 to -70 mV, whereas in the cardiac muscle cells, it is -90 mV. When the membrane voltage reaches this threshold negative charge, reduction of the potassium efflux and slow influx of sodium (funny current) and calcium (T-type calcium channels) occur. This leads to the initiation of spontaneous depolarization during phase 4 of the cardiac action potential. Because this phase corresponds to diastole, it is also called **diastolic depolarization**. When the threshold potential is achieved (-40 mV), phase 0 is triggered mostly through activation of L-type calcium channels. Repolarization occurs during phase 3 when the potassium channels open and calcium channels close. Efflux of potassium causes the return to the resting membrane potential. Once a cell depolarizes, it is no longer excitable, being refractory to all stimuli. After this absolute refractory period, cardiac cells enter a relative refractory period during which only a greater than normal stimuli can cause cardiac cell membranes to depolarize ([Figure 15.21](#)).

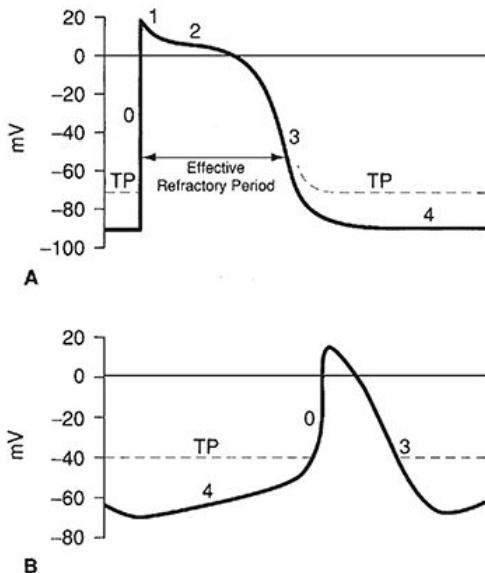


FIGURE 15.21 Cardiac action potential recorded from a ventricular contractile cell (A) or an atrial pacemaker cell (B). TP, threshold potential.

Excitability

Excitability is the ability of the cardiac cell to respond to a stimulus by depolarizing. A measure of excitability is the difference between the resting transmembrane potential and the threshold potential of the cell. The smaller the difference between these potentials, the more excitable or irritable is the cell. Therefore, enhanced automaticity occurs if the threshold potential becomes more negative or the resting membrane potential less negative. The opposite happens in hyperpolarization (Figure 15.22). Acetylcholine released from M_2 receptors during parasympathetic stimulation increases the conductance of the slow potassium channels (the outward flux of potassium). This causes hyperpolarization of the resting membrane potential and increases the membrane potential difference necessary to overcome in order to reach the threshold potential, decreasing excitability. Acetylcholine also decreases the conductance of the sodium channels (influx of sodium), which leads to slower depolarization and decreased automaticity.⁸⁷ Sympathetic stimulation through β_1 receptors increases the conductance of the sodium channels resulting in the depolarization threshold potential being reached more quickly and increased heart rate.

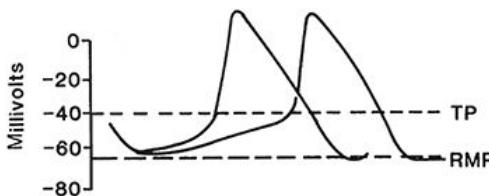


FIGURE 15.22 The rate of pacemaker discharge is dependent on the slope of spontaneous phase 4 depolarization, negativity of the threshold potential (TP), and negativity of the resting transmembrane potential (RMP).

Ectopic Pacemaker

An ectopic pacemaker (abnormal focus) manifests as a premature contraction of the heart that occurs between normal beats. A depolarization wave spreads outward from the ectopic pacemaker and initiates the premature contraction. The ectopic pacemaker may become persistent and assume the role of the dominant pacemaker in place of the SA node. The AV node and the bundle of His are the most common areas for the presence of

an ectopic pacemaker. Impulses generated outside the SA node follow a different pathway in the conduction system (usually slower) generating a change in the configuration of the QRS wave on the ECG.

Types of Dysrhythmias

A systematic approach in reading the ECG is essential for accurate diagnosis and correct treatment. It is important to determine the rate and rhythm, the appearance of the P waves and their relation to the QRS, and the morphology of the QRS complex ([Table 15.5](#)).

TABLE 15.5

Diagnosis of cardiac dysrhythmias from the electrocardiogram

- Are P waves present, and what is their relationship to the QRS complexes?
- Are the amplitudes, durations, and contours of the P waves, P-R intervals, QRS complexes, and Q-T intervals normal?
- During tachycardia, is the R-P long and P-R interval short (or vice versa)?
- What are the atrial and ventricular discharge rates (same or different)?
- Are the P-P and R-R intervals regular or irregular?

Heart Block

Heart block may occur at the SA node, the AV node, or the bundle branches. Causes of heart block include ischemia, age-related degeneration of the conduction system, drug-induced depression of the impulse propagation (digitalis, β -adrenergic antagonists), excessive parasympathetic nervous system stimulation, pressure on the conduction system by atherosclerotic plaques, or direct stimulation of heart by devices such as wires and catheters.

First-degree AV heart block is considered to be present when there is still one-to-one AV conduction but the P-R interval is longer than 0.2 second at a normal heart rate ([Figure 15.23](#)). Second-degree AV heart block is present when some AV conduction still is present but does not occur with every beat. It is classified as Mobitz type I (Wenckebach phenomenon) ([Figure 15.24](#)) or Mobitz type II heart block ([Figure 15.25](#)). Wenckebach phenomenon is characterized by a progressive beat-to-beat prolongation of the P-R interval until conduction of the cardiac impulse is completely interrupted and a P wave is recorded without a subsequent QRS complex. After this dropped beat, the cycle is repeated. Mobitz type II heart block is the occurrence of a nonconducted atrial impulse without a prior change in the P-R interval and is considered a higher degree of AV block than Mobitz type I.



FIGURE 15.23 First-degree atrioventricular block.



FIGURE 15.24 Mobitz type I (Wenckebach). Republished with permission of McGraw Hill LLC from Patel AM. *Lange Instant Access EKGs and Cardiac Studies*. New York, NY: McGraw-Hill, 2010; permission conveyed through Copyright Clearance Center, Inc.



FIGURE 15.25 Mobitz type II. Republished with permission of McGraw Hill LLC from Patel AM. *Lange Instant Access EKGs and Cardiac Studies*. New York, NY: McGraw-Hill, 2010; permission conveyed through Copyright Clearance Center, Inc.

Third-degree AV heart block is present when there is no conduction of beats from the atria to the ventricles. The P waves are dissociated from the QRS complexes, and the heart rate depends on the intrinsic discharge rate of the ectopic pacemaker beyond the site of conduction block. If the ectopic pacemaker is near the AV node, the QRS complexes appear normal and the heart rate is typically 40 to 60 beats per minute ([Figure 15.26](#)). When the site of the block is infranodal, the escape ventricular pacemaker often has a discharge rate of less than 40 beats per minute and the QRS complexes are wide, resembling a bundle branch block ([Figure 15.27](#)).

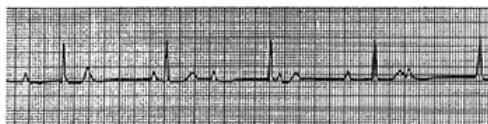


FIGURE 15.26 Third-degree atrioventricular heart block occurring at the level of the atrioventricular node (QRS complexes are narrow). There is no relation between the P waves and QRS complexes.

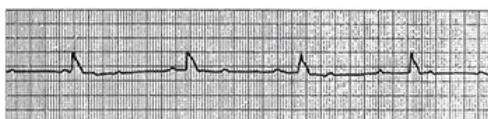


FIGURE 15.27 Third-degree atrioventricular heart block occurring at an infranodal level (QRS complexes are wide).

Patients may experience syncope (Stokes-Adams syndrome) at the onset of third-degree heart block, reflecting the 5- to 10-second period of asystole that may precede the initiation of an ectopic ventricular pacemaker. Occasionally, the interval of ventricular standstill at the onset of third-degree heart block is so long that death occurs. The treatment of patients with third-degree heart block usually requires insertion of a permanent artificial cardiac pacemaker. Temporary support may be provided with intravenous infusion of isoproterenol (chemical cardiac pacemaker) or a transvenous artificial cardiac pacemaker. The safe perioperative management of patients with implanted rhythm control devices such as pacemakers and implantable cardioverter-defibrillators (ICD) requires a basic understanding of the classification, function, and emergency management of these devices.^{[88,89](#)}

Bundle Branch Block

Blockage of the impulse conduction through the right or left bundle branches results in delay of activation of the corresponding ventricle, called **bundle branch block**, which may be complete or incomplete. Hemiblock or fascicular block refers to the blockade of either the anterior or posterior fascicle of the left bundle branch. Left bundle branch block is clinically significant and cardiac disease must be ruled out. Right bundle branch is commonly seen in healthy individuals but may be caused by right heart enlargement from conditions such as atrial septal defect, chronic lung disease, or pulmonary embolism.

Electrocardiographic criteria for complete right bundle branch block ([Figure 15.28](#)) include QRS duration longer than 120 milliseconds; “M-shaped” QRS complex in V₁ and V₂ (RSR'); and slurred S wave in I, aVL, and V₅ and V₆. Complete left bundle branch block ([Figure 15.29](#)) is characterized by QRS longer than 120 milliseconds, M-shaped QRS complex (RSR') in V₆, and QS or RS in V₁.

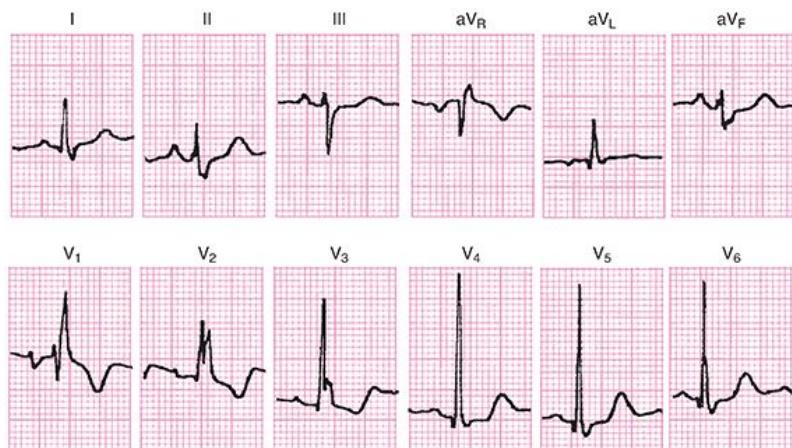


FIGURE 15.28 Right bundle branch block. Reprinted with permission from Badescu GC, Sherman BM, Zaidan JR, et al. *Atlas of electrocardiography*. In: Barash PG, Cullen BF, Stoelting RK, et al., eds. Clinical Anesthesia. 7th ed. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2013:1701-1720.

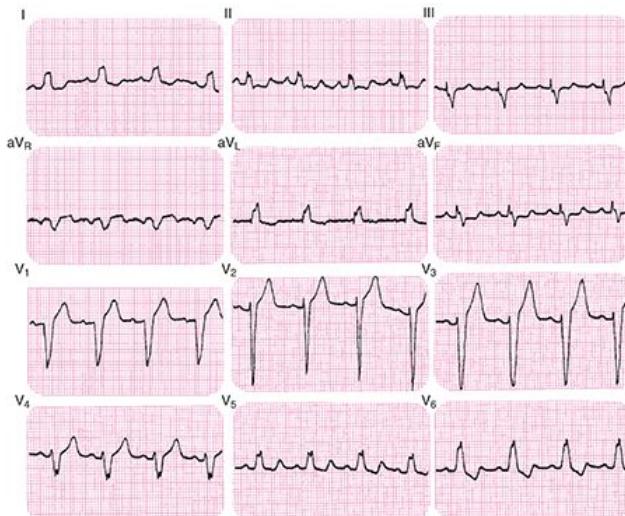


FIGURE 15.29 Left bundle branch block. Reprinted with permission from Badescu GC, Sherman BM, Zaidan JR, et al. *Atlas of electrocardiography*. In: Barash PG, Cullen BF, Stoelting RK, et al., eds. Clinical Anesthesia. 7th ed. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2013:1701-1720.

Reentry

A reentry circuit is the most likely mechanism for supraventricular tachycardia, atrial flutter, atrial fibrillation, premature ventricular contractions, ventricular tachycardia, and ventricular fibrillation. Reentry (circus movements) occurs when the same cardiac impulse returns to its site of initiation through a circuitous pathway and reexcites the cardiac tissue.⁹⁰ This contrasts with automaticity, where each beat is initiated by a new impulse. Reentry circuits can develop at any place in the heart where there is an imbalance between conduction and refractoriness creating a slow and fast pathway. Causes of this imbalance include elongation of the conduction pathway such as occurs in dilated hearts (especially a dilated left atrium associated with mitral stenosis), decreased velocity of conduction of cardiac impulses as occurs with myocardial ischemia or hyperkalemia, and a shortened refractory period of cardiac muscle as produced by epinephrine or electric shock from an alternating current. Each of these conditions creates a situation in which cardiac impulses

conducted by normal Purkinje fibers can return retrograde through abnormal Purkinje fibers that are not in a refractory state (a reentry circuit). Reentry circuits can be eliminated by speeding conduction through normal tissues so cardiac impulses reach their initial site of origin when the fibers are still refractory or by prolonging the refractory period of normal cells so the returning impulses cannot reenter.

Preexcitation Syndrome

A preexcitation syndrome is present when atrial impulses bypass the AV node through an abnormal conduction pathway to produce premature excitation of the ventricle. Normally, the ventricles are protected from rapid atrial rates by the refractory period of the AV node. The most common accessory conduction pathway producing a direct connection (anatomic loop) of the atrium to the ventricle is known as **Kent bundle** (usually left atrium to left ventricle) ([Table 15.6](#)).⁹¹ Conduction via this accessory pathway produces the Wolff-Parkinson-White syndrome, most often manifesting as intermittent bouts of supraventricular tachyarrhythmias. Electrocardiographic features include short P-R interval (<0.12 second), slurring of the QRS (δ wave), and widening of the QRS (>0.12 second). Patients with preexcitation syndrome who are asymptomatic or have no history of tachyarrhythmia usually do not require treatment. According to the American College of Cardiology, avoiding medications that block the conduction through the AV node is recommended, as this may lead to promote anterograde conduction through the accessory pathway.⁹² Medications that slow the conduction down the pathologic pathway (procainamide, flecainide) are preferred. Elimination of the pathologic conduction pathway can be achieved with radiofrequency catheter ablation.⁹³

TABLE 15.6

Accessory pathways and preexcitation syndromes

Connections	
Kent bundle	Atrium to ventricle
Mahaim bundle	Atrioventricular node to ventricle
Atriohisian fiber	Atrium to His bundle
James fiber	Atrium to atrioventricular node

Adapted from Atlee JL. Perioperative cardiac dysrhythmias: diagnosis and management. *Anesthesiology*. 1997;86:1397-1424.

Sinus Tachycardia

Sinus tachycardia is usually defined as a sinus rhythm with a resting heart rate of greater than 100 beats per minute ([Figure 15.30](#)). A common cause of sinus tachycardia is sympathetic nervous system stimulation such as may occur during a noxious stimulus in the presence of low concentrations of anesthetic drugs.

Hyperthermia increases heart rate approximately 18 beats per minute for every degree Celsius increase. Other important causes of sinus tachycardia include hypoxia, hypercarbia, hypovolemia, drugs, hormones, and intrinsic cardiac abnormalities.

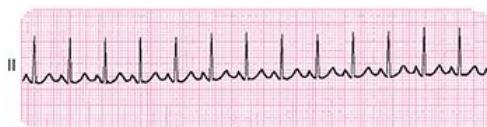


FIGURE 15.30 Sinus tachycardia. Reprinted with permission from Badescu GC, Sherman BM, Zaidan JR, et al. *Atlas of electrocardiography*. In: Barash PG, Cullen BF, Stoelting RK, et al., eds. *Clinical Anesthesia*. 7th ed. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2013:1701-1720.

Sinus Bradycardia

Sinus bradycardia is usually defined as a sinus rhythm with heart rate of less than 60 beats per minute ([Figure 15.31](#)) and may be caused by parasympathetic nervous system (vagal) stimulation of the heart. Other causes

may include hypoxia, medications, and cardiac conditions. Bradycardia that occurs in physically conditioned athletes reflects the ability of their hearts to eject a greater SV with each contraction compared with the less conditioned heart.



FIGURE 15.31 Sinus bradycardia. Reprinted with permission from Badescu GC, Sherman BM, Zaidan JR, et al. *Atlas of electrocardiography*. In: Barash PG, Cullen BF, Stoelting RK, et al., eds. *Clinical Anesthesia*. 7th ed. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2013:1701-1720.

Sinus Dysrhythmias

Sinus dysrhythmia, normal variation in the SA node rate, is present during normal breathing with heart rate (R-R intervals) varying approximately 5% during various phases of the resting breathing cycle ([Figure 15.32](#)). During inspiration, the heart rate increases, and during expiration, it decreases. This variation may increase to 30% during deep breathing. These variations in heart rate with breathing most likely reflect baroreceptor reflex activity and changes in the negative intrapleural pressures that elicit a waxing and waning Bainbridge reflex. Variation in heart rate that is not related to breathing (nonphasic sinus dysrhythmia) is abnormal and may be a result of SA node dysfunction, aging, or digitalis intoxication. In perioperative settings, sinus dysrhythmia is usually transient and often caused by autonomic nervous system imbalance as the result of an intervention (spinal or epidural anesthesia, laryngoscopy, surgical stimulation) or by the effects of drugs on the SA node.

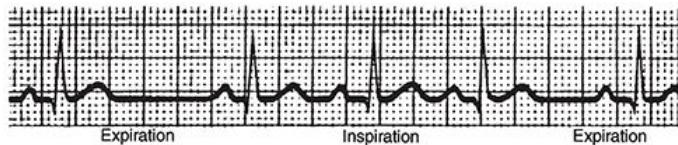


FIGURE 15.32 Sinus dysrhythmia reflecting changes in sinoatrial pacemaker activity with the breathing cycle.

Premature Atrial Contractions

Premature atrial contractions are recognized by an abnormal P wave and a shortened or prolonged P-R interval ([Figure 15.33](#)). The QRS complex of the premature atrial contraction has a normal configuration. The interval between the premature atrial contraction and the succeeding contraction is not an exact multiple of the normal P-P interval (noncompensatory pause) because the SA node is reset. Premature atrial contractions are usually benign and often occur in individuals without heart disease.

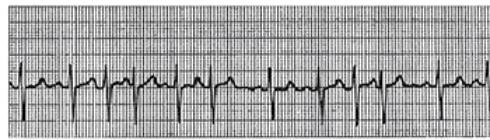


FIGURE 15.33 Premature atrial contractions resulting in an irregular rhythm.

Nodal (Junctional) Paroxysmal Tachycardia

Nodal paroxysmal tachycardia resembles atrial paroxysmal tachycardia except P waves may precede, follow, or be obscured by the QRS complex. It is common following heart surgery. Other causes include ischemia and digitalis intoxication.

Atrial Paroxysmal Tachycardia

Atrial paroxysmal tachycardia, which often occurs in otherwise healthy young individuals, is caused by rapid rhythmic discharges of impulses from an ectopic atrial pacemaker. The rhythm on the ECG is regular and the P waves are abnormal, often inverted, indicating a site of origin other than the SA node ([Figure 15.34](#)). The QRS complex is narrow. The rapid discharge rate of this ectopic focus causes it to become the pacemaker. Typically, the onset of atrial paroxysmal tachycardia is abrupt and may end just as suddenly with the pacemaker shifting back to the SA node. Atrial paroxysmal tachycardia may be terminated by parasympathetic nervous system stimulation of the heart with drugs or by carotid sinus massage. Drugs that increase refractoriness of the AV node (adenosine, calcium channel blockers, β -blockers) are preferred initial therapy for any narrow QRS paroxysmal supraventricular tachycardia.

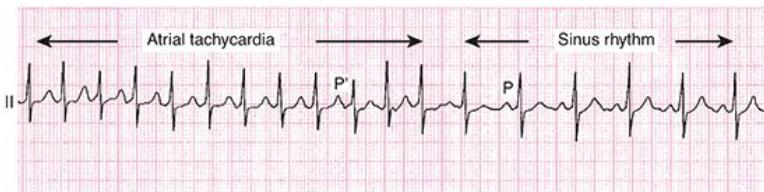


FIGURE 15.34 Atrial paroxysmal tachycardia. Reprinted with permission from Badescu GC, Sherman BM, Zaidan JR, et al. *Atlas of electrocardiography*. In: Barash PG, Cullen BF, Stoelting RK, et al., eds. Clinical Anesthesia. 7th ed. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2013:1701-1720.

Atrial Fibrillation

Atrial fibrillation is characterized by normal QRS complexes occurring at a rapid and irregularly irregular rate in the absence of identifiable P waves ([Figure 15.35](#)). The irregular ventricular response reflects arrival of atrial impulses at the AV node at times that may or may not correspond to the refractory period of the node from a previous discharge. The SV is decreased during atrial fibrillation due to the loss of atrial contraction, which may contribute up to 30% to 40% in ventricular filling depending on the ventricular diastolic status and heart rate.



FIGURE 15.35 Atrial fibrillation. Reprinted with permission from Badescu GC, Sherman BM, Zaidan JR, et al. *Atlas of electrocardiography*. In: Barash PG, Cullen BF, Stoelting RK, et al., eds. Clinical Anesthesia. 7th ed. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2013:1701-1720.

A pulse deficit (heart rate by palpation is less than that of the ECG) reflects the inability of each ventricular contraction to eject a sufficient SV to produce a detectable peripheral pulse. Etiology of atrial fibrillation includes autonomic nervous system stimulation, ischemia, electrolyte imbalance, atrial dilation, infiltration or fibrosis, hyperthyroidism, hypertension, and sleep apnea. There is an estimated 5% annual risk of thromboembolism in patients with atrial fibrillation who are not treated with anticoagulants. Treatment includes rate control therapy, direct current cardioversion, pharmacologic cardioversion (flecainide, dofetilide, propafenone, ibutilide, and amiodarone), catheter ablation, and surgical Maze procedure. Patients with persistent atrial fibrillation should be considered for anticoagulation to prevent left atrial clot and thromboembolism.[94,95](#) The following medications are used for rate control: β -blockers, nondihydropyridine calcium channel antagonists (verapamil, diltiazem), digoxin, and amiodarone.

Atrial Flutter

Atrial flutter is a regular contraction of the atria at a rate of 250 to 300 beats per minute and on the ECG is characterized by 2:1, 3:1, or 4:1 conduction of atrial impulses to the ventricle ([Figure 15.36](#)). This occurs because the functional refractory period of Purkinje fibers and ventricular muscle is such that no more than 200 impulses per minute can be transmitted to the ventricles. The P waves have a characteristic saw-toothed appearance, especially in leads II, III, aVF, and V₁. Atrial flutter is seen commonly in patients with chronic pulmonary disease, dilated cardiomyopathy, myocarditis, ethanol intoxication, and thyrotoxicosis. This dysrhythmia may last minutes to hours before changing to sinus rhythm or atrial fibrillation. Treatment is similar to that of atrial fibrillation.



FIGURE 15.36 Atrial flutter. Reprinted with permission from Badescu GC, Sherman BM, Zaidan JR, et al. *Atlas of electrocardiography*. In: Barash PG, Cullen BF, Stoelting RK, et al., eds. *Clinical Anesthesia*. 7th ed. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2013:1701-1720.

Premature Ventricular Contractions

Premature ventricular contractions result from reentry or an ectopic pacemaker in the ventricles and are not preceded by a P wave. They are classified as unifocal or multifocal based on the morphology of the QRS depending on the number of sites of initiation. The QRS complex of the ECG is widened because the cardiac impulse is conducted through the slowly conducting muscle of the ventricle or an abnormal conduction pathway ([Figure 15.37](#)). The voltage of the QRS complex of the premature ventricular contraction is increased, reflecting the absence of the usual neutralization that occurs when a normal cardiac impulse passes through both ventricles simultaneously. The T wave of premature ventricular contractions usually has an electrical potential opposite that of the QRS complex. A compensatory pause after a premature ventricular contraction occurs because the next impulse from the SA node reaches the ventricle during its refractory period. When a premature ventricular contraction occurs, the ventricle may not have adequately filled to produce a detectable pulse. The subsequent pulse, however, may be increased due to added ventricular filling that occurs during the compensatory pause that typically follows a premature ventricular contraction.



FIGURE 15.37 Multifocal premature ventricular contractions. Reprinted with permission from Badescu GC, Sherman BM, Zaidan JR, et al. *Atlas of electrocardiography*. In: Barash PG, Cullen BF, Stoelting RK, et al., eds. *Clinical Anesthesia*. 7th ed. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2013:1701-1720.

Premature ventricular contractions often reflect significant cardiac disease. For example, myocardial ischemia may be responsible for initiation of premature ventricular contractions from an irritable site in poorly oxygenated ventricular muscle. Other causes include valvular heart disease, high-catecholamine state, hypoxia, hypercapnia, cocaine, alcohol, caffeine, electrolyte abnormalities, and medications. Treatment of premature ventricular contractions includes removal of trigger factors, β -blockers, calcium channel blockers, lidocaine, amiodarone, and radiofrequency ablation depending on the symptoms.

Ventricular Tachycardia

Ventricular tachycardia on the ECG resembles a series of ventricular premature contractions that occur at a rapid (200-300 beats per minute) and regular rate ([Figure 15.38](#)). It is classified as monomorphic or polymorphic and predisposes to ventricular fibrillation. Common causes of ventricular tachycardia are

myocardial ischemia, cardiomyopathies (dilated, hypertrophic, arrhythmogenic right ventricular cardiomyopathy), electrolyte abnormalities (potassium, magnesium, calcium), conditions that result in QT prolongation, drug toxicity, and congenital myocardial defects. The SV is often severely depressed during ventricular tachycardia because the ventricles have insufficient time for cardiac filling. Presentation may include palpitations, shortness of breath, chest pain, presyncope, syncope, and sudden cardiac arrest causing death.⁹⁶



FIGURE 15.38 Ventricular tachycardia. Reprinted with permission from Badescu GC, Sherman BM, Zaidan JR, et al. *Atlas of electrocardiography*. In: Barash PG, Cullen BF, Stoelting RK, et al., eds. Clinical Anesthesia. 7th ed. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2013:1701-1720.

Nonsustained ventricular tachycardia may be defined as three or more consecutive ventricular beats at a rate greater than 100 beats per minute lasting less than 30 seconds and is usually asymptomatic.⁹⁷ Sustained ventricular tachycardia usually leads to hemodynamic instability and necessitates termination with electrical cardioversion. Therapies include correction of electrolyte abnormalities, ICD placement, β -blockers (sotalol, amiodarone), ablation, and revascularization.⁹⁶

Ventricular Fibrillation

Ventricular fibrillation is characterized on the ECG by an irregular wavy line with voltages that range from 0.25 to 0.5 mV (**Figure 15.39**). There is total absence of coordinated contractions with cessation of any effective pumping activity and disappearance of detectable pulse and systemic blood pressure. Ventricular fibrillation is usually initiated by a reentry mechanism. The only effective treatment of ventricular fibrillation is the delivery of direct electric current through the ventricles (defibrillation), which simultaneously depolarizes all ventricular muscle. This depolarization allows the initiation of a cardiac pacemaker remote from the irritable focus responsible for the ventricular fibrillation. Cardiopulmonary resuscitation must be initiated until a defibrillator becomes available. The survival rate of ventricular fibrillation may decrease by 7% to 10% for every minute that defibrillation is delayed, depending on the cardiopulmonary resuscitation quality. If defibrillation is delayed for more than 12 minutes, the survival rate is less than 5%.⁹⁸ It is important to identify the patients at risk for ventricular fibrillation and place a prophylactic ICD.⁹⁶

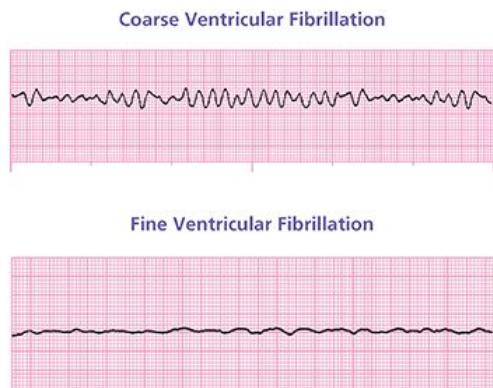


FIGURE 15.39 Ventricular fibrillation. Reprinted with permission from Badescu GC, Sherman BM, Zaidan JR, et al. *Atlas of electrocardiography*. In: Barash PG, Cullen BF, Stoelting RK, et al., eds. Clinical Anesthesia. 7th ed. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2013:1701-1720.

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Renal Physiology*

Updated by: Brian Chang • Jonathan Hastie

The kidneys play a central role in the maintenance of homeostasis of the body. The kidneys stabilize extracellular fluid electrolyte composition, maintain acid-base balance, regulate volume status and blood pressure, secrete erythropoietin and renin, and excrete toxins and metabolic waste. These functions involve complex interactions within the kidneys and with other organ systems and are frequently altered during anesthesia. Hence, a thorough understanding of kidney function is important for the anesthesiologist before, during, and after patients receive care in the operating room.

Kidney Structure and Function

Basic Anatomy of the Kidney

The kidneys are paired organs located below the diaphragm in the retroperitoneal space, weighing between 115 and 160 g each. Each kidney has an outer portion (cortex) and inner portion (medulla). The renal arteries arise from the abdominal aorta, and the renal veins direct blood flow into the inferior vena cava. The kidneys are prominently innervated by the sympathetic nervous system from T4 to T12.

The nephron is the functional unit of the kidney ([Figure 16.1](#)). A nephron is composed of a capillary bed called the **glomerulus** surrounded by epithelial cells called **Bowman capsule**. Bowman capsule, in turn, is continuous with a long tubule that drains into the renal pelvis. Fluid is filtered through the glomerular capillaries and is converted, along the length of the renal tubule, into urine.¹ There are two types of nephrons: Juxtamedullary nephrons are located near the corticomedullary border and have long tubules that descend deep into the renal medulla, whereas cortical nephrons are closer to the surface of the kidney and have shorter tubules that only penetrate the outer portion of the renal medulla.

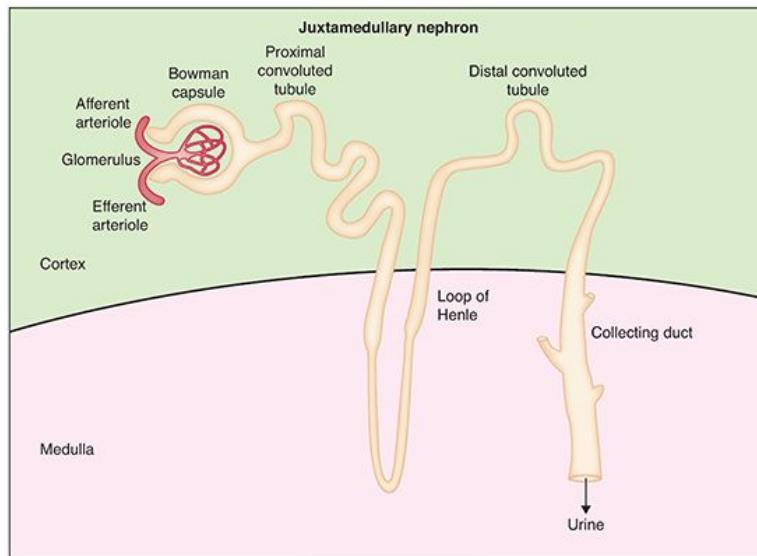


FIGURE 16.1 Schematic depiction of a juxtamedullary nephron.

The Glomerulus

Structure and Function of the Glomerulus

Glomeruli are found in the renal cortex and consist of a tuft of capillaries surrounded by Bowman capsule, the dilated blind end of the renal tubule. Glomerular capillaries are uniquely interposed between two sets of arterioles. Blood flows from the afferent arterioles through the glomerular capillaries and then on to the efferent arterioles. Hence, pressure in the glomerular capillaries is a function of the vascular activity of both the afferent and efferent arterioles ([Figure 16.2](#)): Afferent vasoconstriction lowers glomerular capillary pressure, whereas efferent arteriolar vasoconstriction raises glomerular capillary pressure. Glomerular capillary pressure causes water and low molecular weight substances to be filtered into Bowman capsule and the renal tubule system.

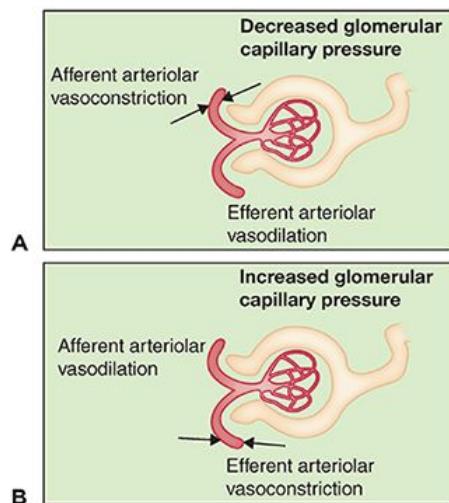


FIGURE 16.2 Glomerular filtration pressure. A, Afferent arteriolar vasoconstriction decreases glomerular capillary pressure and hence decreases glomerular filtration rate (GFR). B, Efferent arteriolar vasoconstriction increases glomerular capillary pressure and hence increases GFR.

Fluid that is filtered from the glomerular capillaries into the renal tubules is called **glomerular filtrate**. The permeability of the glomerular capillary membrane is much greater than that of the typical tissue capillary. Fluid, amino acids, and ions are rapidly filtered, whereas higher molecular weight proteins are retained within the capillary.

Glomerular Filtration Rate

The volume of collective glomerular filtrate formed over time is called the **glomerular filtration rate (GFR)**. In a normal person, the GFR is approximately 125 mL per minute or 180 L per day. Because 99% of this 180 L of glomerular filtrate is reabsorbed, daily urine output is 1 to 2 L. As described earlier, glomerular capillary pressure leads to filtration into the renal tubule. The normal filtration pressure of approximately 10 mm Hg is calculated as glomerular capillary pressure (60 mm Hg) minus colloid osmotic pressure (32 mm Hg) and pressure in Bowman capsule (18 mm Hg) ([Figure 16.3](#)). The filtration rate is influenced by several factors. Mean arterial pressure, cardiac output, and the sympathetic nervous system may each raise glomerular capillary pressure, thus increasing the GFR.

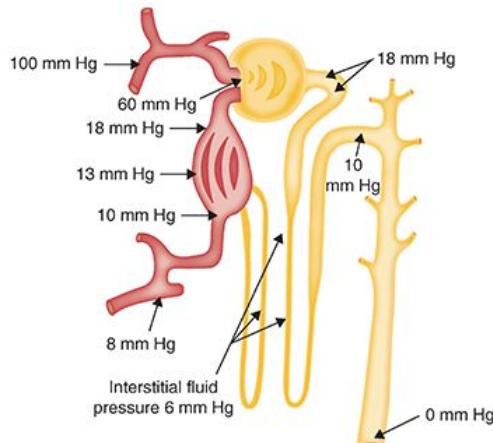


FIGURE 16.3 Intravascular pressures in the renal circulation. Reprinted from Guyton AC, Hall JE. Textbook of Medical Physiology. 10th ed. Philadelphia, PA: W.B. Saunders; 2000. Copyright © 2000 Elsevier. With permission.

The kidneys have an autoregulatory mechanism to modulate the effect of mean arterial pressure on the GFR. This process of autoregulation involves feedback from the distal renal tubules to the glomerulus. Specialized epithelial cells in the distal renal tubules, called the **macula densa**, signal the afferent or efferent renal arterioles to either vasoconstrict or vasodilate. Through the consequent adjustment of glomerular capillary pressure, a nearly constant filtration pressure leads to a consistent GFR across a range of mean arterial pressure, remaining relatively constant between mean arterial pressures of 60 and 160 mm Hg. Because even a small change in GFR can lead to wide variations in urine output, it is clear that tubule-glomerular feedback serves an important role in homeostasis.

The Renal Tubule

Structure of the Renal Tubule

The renal tubule is composed of the proximal convoluted tubule, the loop of Henle, and the distal convoluted tubule (see [Figure 16.1](#)).¹ As described earlier, the loops of Henle in juxamedullary nephrons extend into the renal medulla before returning filtrate back to the renal cortex in the distal convoluted tubule. Glomerular filtrate, after passing along the length of the renal tubule, then enters the collecting duct, which is a confluence of filtrate from several nephrons into the renal pelvis.

Renal Tubular Function

Glomerular filtrate is converted into urine along the course of the renal tubule ([Table 16.1](#)).² The majority of water and various solutes that are filtered by glomerular capillaries are reabsorbed into peritubular capillaries. Metabolic waste products, also filtered by glomerular capillaries, are not reabsorbed. Other solutes are secreted by renal tubular epithelial cells into the lumen of the renal tubule. Thus, the urine found in the collecting duct is composed mainly of substances filtered through the glomerular capillaries and a small amount of secreted substances. The process of reabsorption determines the volume of urine formed, whereas secretion is particularly important in determining the nature of the urine, such as concentration of potassium and hydrogen ions. Various portions of the renal tubule have differing roles in reabsorption and secretion (see [Table 16.1](#)).² Approximately two-thirds of all reabsorption and secretion in the renal tubules occurs in the proximal renal tubules. The most important factors influencing the reabsorption of sodium and water are aldosterone, arginine vasopressin (AVP), renal prostaglandins, and atrial natriuretic peptide.

TABLE 16.1

Magnitude and site of solute reabsorption or secretion in the renal tubules

Filtered (24)	Reabsorbed (24)	Secreted (24)	Excreted (24)	%	Location
---------------	-----------------	---------------	---------------	---	----------

	hours)	hours)	hours)	hours)	Reabsorbed	
Water (L)	180	179	—	1	99.4	P, L, D, C
Sodium (mEq)	26,000	25,850	—	150	99.4	P, L, D, C
Potassium (mEq)	600	560	50	90	93.3	P, L, D, C
Chloride (mEq)	18,000	17,850	—	150	99.2	P, L, D, C
Bicarbonate (mEq)	4,900	4,900	—	0	10	P, D
Urea (mM)	870	460	—	410	53	P, L, D, C
Uric acid (mM)	50	49	4	5	98	P
Glucose (mM)	800	800	—	0	100	P

Abbreviations: C, convoluted tubule; D, distal tubule; L, loop of Henle; P, proximal tubule.

Reabsorption of sodium involves moving this ion against a concentration gradient from the lumen of the proximal tubule into peritubular capillaries. This process requires energy, supplied by the sodium-potassium adenosine triphosphatase (ATPase) system. Other transport processes along the tubule, including glucose reabsorption, amino acid reabsorption, and organic acid secretion, share a common carrier with sodium. Hence, the great majority of transport across renal tubular cells is dependent on sodium-potassium ATPase activity. Given this dependence on the sodium-potassium ATPase, the proximal convoluted renal tubules consume approximately 80% of renal oxygen consumption.³

More than 99% of the water in the glomerular filtrate is reabsorbed into peritubular capillaries as it passes through renal tubules. The variation in permeability of epithelial cells lining the tubules is important in renal function. Rapid osmosis of water through proximal renal tubules means that the concentration of solutes on the capillary side of cell membranes is almost never more than a few milliosmoles greater than in the tubular lumen. However, the distal tubules are almost completely impermeable to water, allowing for control of the specific gravity of the urine. The permeability of the collecting ducts is variable and determined by the action of AVP. When AVP activates adenylate cyclase in the epithelial cells lining the collecting duct, the resulting cyclic adenosine monophosphate increases permeability of cell membranes to water via aquaporins. Hence, increased AVP leads to reabsorption of water from the collecting ducts and small amounts of highly concentrated urine. Decreased AVP results in little water reabsorption and large amounts of dilute urine.

Countercurrent System

The ability of the kidneys to produce either dilute or concentrated urine depends on the osmolarity gradient between the renal cortex and renal medulla that is created by the loop of Henle. Whereas the renal cortex has a relatively low osmolarity (300 mOsm/L), the renal medulla contains highly concentrated interstitial fluid (1,400 mOsm/L near the renal pelvis) due to active reabsorption of solutes in the loop of Henle ([Figure 16.4](#)).³ The high medullary osmolarity is maintained in part by sluggish blood flow, preventing the removal of solutes.

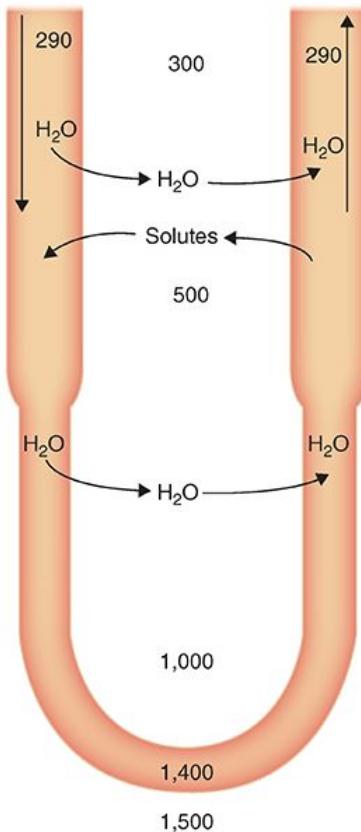


FIGURE 16.4 Countercurrent exchange of water and solutes in the vasa recta. Adapted from Lote CJ, Harper L, Savage CO. Mechanisms of acute renal failure. Br J Anaesth. 1996;77(1):82-89 and Lote CJ. Principles of Renal Physiology. 3rd ed. London: Chapman and Hall; 1994. Copyright © 1996 Elsevier. With permission.

Just as the juxamedullary loops of Henle carry glomerular filtrate from the cortex into the renal medulla and back to the cortex, the vascular supply has a similar structure. The U-shaped arrangement of peritubular capillaries, known as the **vasa recta**, parallels the loops of Henle. This forms a countercurrent system, in which capillary inflow runs parallel and in an opposite direction to capillary outflow.

Aquaporins

The high osmolarity in the renal medulla allows for the potential for quick reabsorption of water by osmosis as filtrate passes through the renal collecting ducts. This process is mediated by aquaporins, which are channels that facilitate rapid passage of water across lipid cell membranes at a velocity greater than possible by simple diffusion.⁴⁻⁶ They are tetramer protein structures and are found in the kidneys, brain, salivary and lacrimal glands, and respiratory tract. Five aquaporins in the kidney have a role in water balance.⁵ Aquaporin 1 is in the proximal renal tubules, whereas aquaporin 2 is found in the renal collecting ducts. In response to AVP, the channels in the tubular collecting duct epithelium are opened, leading to reabsorption of water and formation of concentrated urine. In the absence of AVP, dilute urine travels through the collecting ducts without being affected by medullary osmolarity.

Tubular Transport Maximum

Tubular transport maximum (T_{max} or T_{max}) is the maximum amount of a substance that can be actively reabsorbed from the lumens of renal tubules each minute. The T_{max} depends on the amounts of carrier substance and enzyme available to the specific active transport system in the lining epithelial cells of renal tubules.

For example, the T_{max} for glucose is approximately 220 mg per minute. When the amount of glucose that filters through the glomerular capillary exceeds this amount, the excess glucose cannot be reabsorbed and passes into urine ([Figure 16.5](#)). The usual amount of glucose in the glomerular filtrate entering proximal renal tubules is 125 mg per minute, and there is no detectable loss into urine. When the tubular load, however, exceeds approximately 220 mg per minute (threshold concentration), glucose begins to appear in urine. A blood glucose concentration of 180 mg/dL in the presence of a normal GFR results in delivery of 220 mg per minute of glucose into the renal tubular fluid. Loss of glucose in urine occurs at concentrations above the T_{max} for glucose. The presence of large amounts of unreabsorbed solutes in the urine such as glucose (or mannitol) produces osmotic diuresis by retaining water in the collecting duct system.

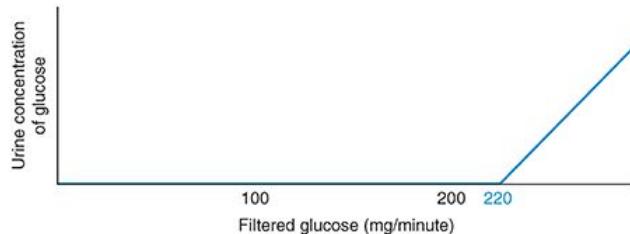


FIGURE 16.5 Transport maximum for glucose. Urinary concentration of glucose is negligible until the amount of filtered glucose exceeds the transport maximum.

Transport of Urine to the Bladder

From the collecting ducts, urine travels into the renal pelvis. A ureter arises from the pelvis of each kidney. At its distal end, the ureter penetrates the bladder obliquely such that pressure in the bladder compresses the ureter, thereby preventing reflux of urine into the ureter when bladder pressure increases during micturition.

Each ureter is innervated by the sympathetic and parasympathetic nervous system. As urine collects in the renal pelvis, the pressure in the pelvis increases and initiates a peristaltic contraction that travels downward along the ureter to force urine toward the bladder. Parasympathetic nervous system stimulation increases the frequency of peristalsis, whereas sympathetic nervous system stimulation decreases peristalsis.

Obstruction of a ureter by a stone causes intense reflex constriction and pain. This pain elicits a sympathetic nervous system reflex (ureterorenal reflex) that causes vasoconstriction of the renal arterioles and a concomitant decrease in urine formation in the kidney.

As the bladder fills with urine, stretch receptors in the bladder wall initiate micturition contractions. Sensory signals are conducted to the sacral segments of the spinal cord through the pelvic nerves and then back again to the bladder through parasympathetic nervous system fibers. The micturition reflex is a completely automatic spinal cord reflex that can be inhibited (tonic contraction of the external urinary sphincter) or facilitated by centers in the brain. Spinal cord damage above the sacral region leaves the micturition reflex intact but severs the connection to the brain.

Renal Blood Flow

Although the kidneys represent about 0.5% of total body weight, their blood flow is disproportionately large at 20% to 25% of the cardiac output.³ Renal blood flow is approximately 400 mL/100 g per minute, compared with 70 mL/100 g per minute for the heart and liver. Autoregulation keeps renal blood flow relatively constant across a range of systemic mean arterial pressures. Because renal blood flow is large, the fraction of oxygen extraction is low despite high oxygen consumption. The PO_2 decreases from 95 mm Hg in the renal artery to about 70 mm Hg in the renal vein.

Approximately 90% of the renal blood flow is distributed to the renal cortex, with less than 10% of renal blood flow going to the medulla. The generous delivery of blood to the cortex supports flow-dependent functions such as glomerular filtration and tubular reabsorption processes of the cortex. By contrast, low blood flow in the medulla maintains a high interstitial fluid osmolarity, which in turn permits concentration of the urine.⁷ Low blood flow also makes the medulla more susceptible to ischemia than the cortex.

Renal Cortex Blood Flow: Glomerular and Peritubular Capillaries

Blood enters the renal artery, whose branches ultimately supply the afferent arterioles of the glomeruli. As described earlier, afferent arterioles feed the glomerular capillary bed (see [Figure 16.1](#)).¹ The pressure in the glomerular capillary bed can be raised by an increase in the vascular resistance of the efferent arterioles. Increased glomerular capillary pressure increases filtration of fluid into Bowman capsule. Blood also flows from the arterioles into a second capillary network called **peritubular capillaries**. These capillaries have substantially lower pressure (see [Figure 16.3](#)),⁸ promoting reabsorption of fluid from the tubules into the peritubular capillaries.

Renal Medulla Blood Flow: The Vasa Recta

The **vasa recta**, described earlier in the countercurrent system, receive only 1% to 2% of renal blood flow. These capillaries, after descending into the renal medulla, return to the renal cortex and empty into veins. As described earlier, this countercurrent system minimizes the washout of solutes from the interstitial fluid of the medulla creating a high osmolarity that promotes the absorption of water from the collecting ducts and the formation of concentrated urine.

Autoregulation of Renal Blood Flow

As noted previously, autoregulation keeps renal blood flow and GFR relatively constant within a range of mean arterial pressure between approximately 60 and 160 mm Hg ([Figure 16.6](#)).⁸ Because the GFR parallels renal blood flow, cardiac output has an important effect on the GFR. The mechanism for autoregulation is controversial.⁹ One theory is a myogenic response, whereby increased perfusion pressure leads to an increased wall tension in the afferent arterioles, resulting in automatic contraction of the smooth muscle fibers in the vessel wall. This increases resistance, keeping flow constant despite the increase in perfusion pressure.³ An alternative hypothesis is that a tubuloglomerular feedback mechanism is responsible for autoregulation, whereby increased perfusion pressure will increase filtration, increasing the tubular fluid delivery to the macula densa, which then releases a factor or factors that cause vasoconstriction.

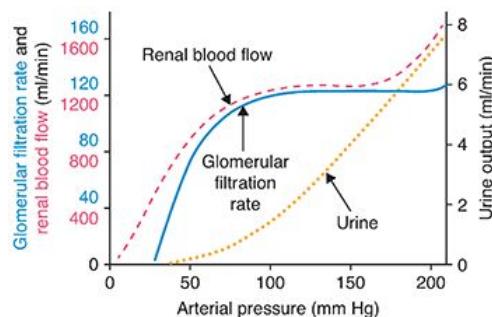


FIGURE 16.6 Autoregulation. Renal blood flow and glomerular filtration rate, but not urine output, are autoregulated between a mean arterial pressure of approximately 60 and 160 mm Hg. Reprinted from Guyton AC, Hall JE. Textbook of Medical Physiology. 10th ed. Philadelphia, PA: W.B. Saunders; 2000. Copyright © 2000 Elsevier. With permission.

In the setting of decreased effective circulating volume, however, renal blood flow may be decreased despite adequate perfusion pressure. Activation of the sympathetic nervous system shunts cardiac output away from the kidneys. Hence, adequate systemic blood pressure does not necessarily indicate adequate renal perfusion in the presence of hypovolemia.

Juxtaglomerular Apparatus

The juxtaglomerular apparatus is where the distal renal tubule passes between the afferent and efferent arterioles and is composed of the macula densa and juxtaglomerular cells. In response to decreased renal blood flow, juxtaglomerular cells release renin into the circulation ([Figure 16.7](#)).³ Renin converts angiotensinogen to angiotensin I, which is then converted to angiotensin II by angiotensin-converting

enzyme. Effects of angiotensin II include thirst, vasoconstriction, and salt and water reabsorption by the kidneys to maintain circulating volume and increase renal blood flow. Whether the initial cause of decreased renal blood flow is the result of hypovolemia, systemic hypotension, or sympathetic nervous system stimulation, the effect of renin is to maintain renal blood flow and GFR.

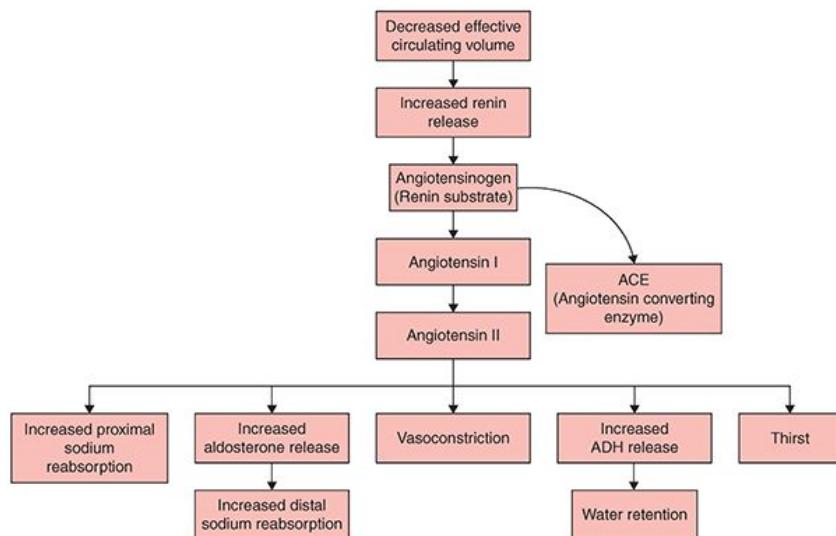


FIGURE 16.7 The role of the renin-angiotensin system in the maintenance of effective circulating volume. Abbreviation: ADH, antidiuretic hormone. Reprinted from Lote CJ, Harper L, Savage CO. Mechanisms of acute renal failure. Br J Anaesth. 1996;77(1):82-89; Copyright © 1996 Elsevier. With permission.

Regulation of Body Fluid

The kidneys have a primary role in the regulation of the amount and nature of body fluids. They control the following characteristics:

- Blood and extracellular fluid volume
- Osmolarity of body fluids
- Plasma concentration of ions and urea

Blood and Extracellular Fluid Volume

Blood volume is maintained over a narrow range despite large daily variations in fluid and solute intake or loss. The mechanism for control of blood volume also affects systemic blood pressure and cardiac output. An increase in blood volume increases the cardiac output, which usually increases the systemic blood pressure. Increased cardiac output and systemic arterial pressure will increase renal blood flow and GFR, resulting in an increase in urine output. The negative feedback loop is completed by a consequent decrease in circulating blood volume.

This basic regulatory mechanism is augmented by other factors. In the setting of decreased blood volume, an increased circulating concentration of AVP will increase water reabsorption, whereas an increase in aldosterone will promote sodium reabsorption and thus an osmotic reabsorption of water. This decreases urine volume and restores blood volume. Another factor is mediated through atrial stretch receptors and atrial natriuretic peptide to be described in the next section.

Regulation of normal circulating blood volume is impaired by factors directly affecting vascular capacitance. Persistent vasoconstriction associated with essential hypertension or sympathetic nervous system stimulation (eg, pheochromocytoma) results in a decrease in blood volume. Conversely, blood volume may be increased by chronic drug-induced vasodilation or the effects of severe varicose veins.

The regulation of extracellular fluid volume is controlled indirectly through the maintenance of circulating blood volume. An increase in blood volume leads to an increase in extracellular fluid volume,

whereas decreased extracellular fluid volume accompanies reduced blood volume. Although these volumes move in the same direction, their proportional change is affected by capillary permeability, which is commonly influenced by perioperative factors. Oxidative injury, ischemia/reperfusion injury, hypervolemia, and significant blood loss, damage the endothelial glycocalyx, which plays an important role in regulating vascular permeability.¹⁰ The extracellular fluid space may be considered as a reservoir for excess intravenous fluid administered during the perioperative period.

Atrial and Renal Natriuretic Factors

Cardiac atrial muscle synthesizes and secretes a peptide hormone known as **atrial natriuretic peptide** (ANP), which is released in response to increased right and left atrial pressure and volume. The ANP binds to receptors in the renal collecting ducts and, acting via transcellular second messenger systems, inhibits sodium reabsorption. Hence, atrial “stretch” promotes elimination of sodium and water, and a subsequent decrease in circulating volume. The ANP additionally has vasodilatory properties, thereby lowering systemic blood pressure and eliciting renal artery vasodilation.

The renal analogue of ANP is renal natriuretic peptide (urodilatin), which is synthesized in renal cortical nephrons. It is likely that ANP is primarily a cardiovascular regulator and relatively unimportant for sodium excretion, whereas renal natriuretic peptide participates in the intrarenal regulation of sodium excretion.^{3,11} In mechanical ventilation, positive end-expiratory pressure reduces atrial distension and atrial transmural pressure, by decreasing venous return. This reduces ANP release, which may contribute to sodium and water retention by the kidneys in patients who are mechanically ventilated.

Osmolarity of Body Fluids

The primary determinant of body fluid osmolarity is the concentration of sodium in the extracellular fluid. Sodium ion concentration is largely controlled by two mechanisms: the osmoreceptor-AVP response and the thirst reflex. Aldosterone, by contrast, has a minimal role in the maintenance of sodium concentration and plasma osmolarity ([Figure 16.8](#)).⁸ Aldosterone-induced reabsorption of sodium is accompanied by reabsorption of water. For this reason, patients with primary hyperaldosteronism typically have increased extracellular fluid volume but nearly normal serum sodium levels.

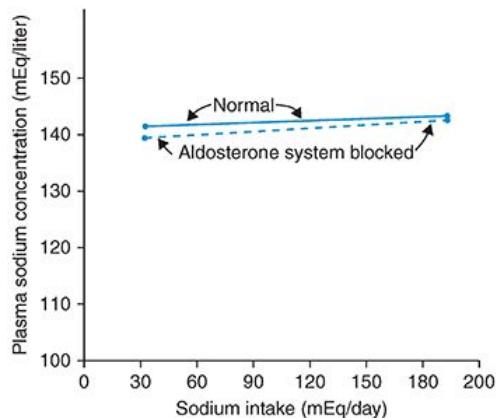


FIGURE 16.8 In the absence of aldosterone, the plasma concentration of sodium varies less than 2% over a sixfold range in sodium intake. Reprinted from Guyton AC, Hall JE. Textbook of Medical Physiology. 10th ed. Philadelphia, PA: W.B. Saunders; 2000. Copyright © 2000 Elsevier. With permission.

Osmoreceptor–Arginine Vasopressin Hormone

In response to increased extracellular fluid osmolarity, osmoreceptors in the hypothalamus signal the posterior pituitary to increase the release of AVP. The AVP is also secreted in the setting of water deprivation and hemorrhage. Circulating AVP causes collecting ducts to reabsorb water, thus decreasing serum sodium levels. Decreased sodium levels result in a decrease in serum osmolarity. The inverse is also true. Abnormally low

extracellular fluid osmolality will lead to a decrease in the release of AVP, thereby increasing the production of dilute urine. This increases serum sodium and osmolarity toward normal. A small change in osmolarity (as little as 1%) can produce a large change in circulating AVP concentration, producing tight regulation of serum osmolality.

Thirst Reflex

The thirst reflex is primarily elicited by an increase in sodium concentration in the extracellular fluid. An increase in sodium as small as 2 mEq/L above normal (or an increase in osmolarity of approximately 4 mOsm/L) will stimulate thirst, and water consumption decreases sodium concentration toward normal. In this way, extracellular fluid osmolarity is maintained within a narrow range. In addition, angiotensin II promotes a thirst response, so circulatory changes that increase the production of angiotensin II, such as acute hemorrhage or congestive heart failure, will increase thirst.

Plasma Concentration of Ions and Urea

Sodium

The kidneys control the concentration of sodium through the process of reabsorption. As described earlier, active transport moves sodium ions from the tubular lumen into the peritubular capillaries. Two-thirds of the sodium in glomerular filtrate is reabsorbed in the proximal renal tubule, and less than 10% of sodium is expected to reach the distal renal tubule. The renin-angiotensin-aldosterone system (RAAS) modulates the sodium reabsorption via the renal tubules. Hypotension or decreased circulating blood volume activates the RAAS, increasing levels of angiotensin II, which ultimately results in increased sodium reabsorption.

Angiotensin II leads to efferent arteriole vasoconstriction, increasing glomerular capillary pressure and GFR. It also increases secretion of aldosterone, which exerts its effect in the distal renal tubule. When aldosterone levels are increased, nearly all the remaining sodium is reabsorbed from the distal tubule, and urinary excretion of sodium is negligible. Typically, only 1% of the filtered sodium is excreted in the urine (see [Table 16.1](#)).²

Potassium

Potassium, after being filtered through the glomerulus, is then reabsorbed by the proximal tubule and loop of Henle. Potassium is either reabsorbed or secreted in the distal tubule and collecting duct, depending on the level of aldosterone. An increase in aldosterone increases potassium ion secretion into the renal tubules and consequently increases urinary potassium. The feedback mechanism allows for close regulation: Small changes in potassium concentration will lead to a substantial change in the concentration of aldosterone ([Figure 16.9](#)).⁸ When aldosterone activity is inhibited by certain diuretics (ie, spironolactone and eplerenone), plasma potassium concentration depends more on dietary intake of potassium, making hypokalemia or hyperkalemia more likely ([Figure 16.10](#)).⁸

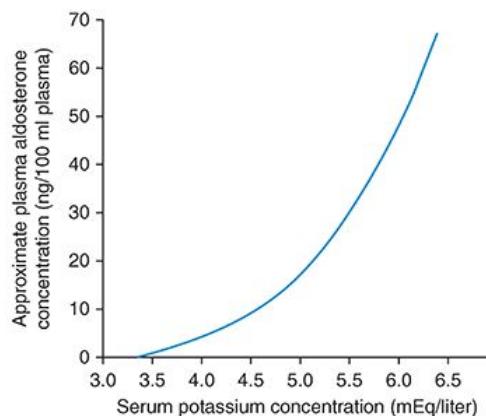


FIGURE 16.9 Small changes in the plasma concentrations of potassium evoke large changes in the plasma concentration of aldosterone. *Reprinted from Guyton AC, Hall JE. Textbook of Medical Physiology. 10th ed.*

Philadelphia, PA: W.B. Saunders; 2000. Copyright © 2000 Elsevier. With permission.

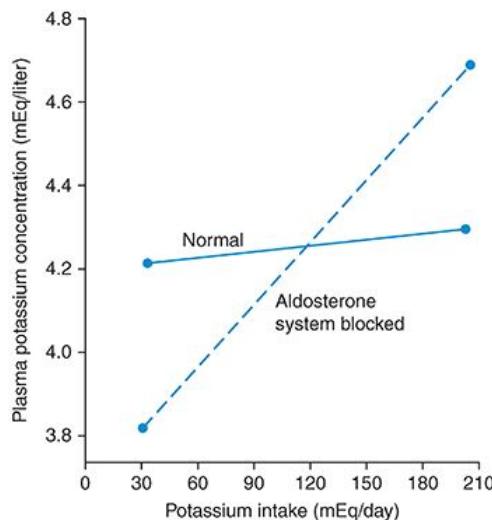


FIGURE 16.10 Plasma concentrations of potassium parallel intake when aldosterone activity is impaired.
Reprinted from Guyton AC, Hall JE. Textbook of Medical Physiology. 10th ed. Philadelphia, PA: W.B. Saunders; 2000. Copyright © 2000 Elsevier. With permission.

The regulation of sodium and hydrogen ion concentrations also has an effect on urinary excretion of potassium. Hydrogen ions compete with potassium for secretion into the renal tubules. In the presence of alkalosis (eg, vomiting and loss of gastric acid), potassium is excreted in the urine in order to maintain acid-base balance. Conversely, a metabolic acidosis will lead to the secretion of hydrogen ions and retention of potassium, and plasma potassium concentration will increase. Sodium intake may influence plasma concentrations of potassium because sodium is transported through renal tubular epithelial cells in exchange for potassium.

Acid-Base Balance

The kidneys secrete excess hydrogen ions by exchanging a hydrogen ion for a sodium ion, thus acidifying the urine, and by the synthesis of ammonia, which combines with hydrogen to form ammonium. In the presence of hypovolemia, bicarbonate reabsorption by the kidneys will lead to acidification of the urine and a metabolic alkalosis.

Calcium and Magnesium

Calcium ion concentration is controlled principally by the effect of parathyroid hormone on bone reabsorption, which releases calcium. Additionally, parathyroid hormone increases the reabsorption of calcium from the distal renal tubules and collecting ducts. Magnesium is reabsorbed by all portions of the renal tubules. Urinary excretion of magnesium parallels the plasma concentration of this ion.

Urea

Urea is the most abundant metabolic waste product. Without adequate clearance of urea, excessive accumulation in body fluids prevents normal function of multiple systems. Urea elimination depends on the plasma concentration of urea (blood urea nitrogen or BUN) and the GFR. Approximately 50% of the urea that is filtered into the renal tubules is eliminated in the urine; the remainder is reabsorbed. When the GFR is low, tubular filtrate flow is relatively slow, thus increasing the proportion of urea that is reabsorbed. This effectively increases the BUN by decreasing urinary elimination of urea. Conversely, when GFR increases, less urea is reabsorbed in the tubules, increasing its elimination in the urine, and BUN decreases.

Measuring Kidney Function

Formal measurement of kidney function requires labor-intensive studies such as collection of urine over time and measurement of blood and urine components. For clinical decision making, estimates of GFR are accessible and inexpensive, requiring only basic laboratory work. Serum creatinine (SCr), commonly used to measure changes in kidney function, is insensitive to small changes in GFR; GFR needs to decrease by about 50% before a rise in SCr is seen. For many years, the Cockcroft-Gault formula has been used to estimate GFR.¹²

$$\text{GFR}_{\text{men}} = (140 - \text{age}) \times \text{weight (kg)} / \text{serum creatinine (mg/dL)} \times 72$$

$$\text{GFR}_{\text{women}} = (140 - \text{age}) \times \text{weight (kg)} \times 0.85 / \text{serum creatinine (mg/dL)} \times 72$$

The difference in the formula between men and women accounts for the expected difference in muscle mass and creatinine production. The formula also takes into account the effect of age on GFR. Given an age-related decrease in muscle mass, GFR in an elderly person will typically be less than a younger person with the same weight and SCr.

The Modification of Diet in Renal Disease formula uses four variables to estimate GFR: age, SCr, ethnicity, and gender, and is independent of body weight.¹³ Developed in a population of patients with chronic kidney disease in the United States, it has been widely adopted as a useful estimate of GFR, although questions remain concerning its applicability to other populations. Both Cockcroft-Gault and Modification of Diet in Renal Disease assume steady-state conditions: balanced production and clearance of SCr leading to a consistent concentration. Because an acute reduction in GFR will result in a rise in SCr over many hours or days, these formulas are poor measures of GFR in acute kidney injury (AKI).

Acute Kidney Injury

The AKI results in an abrupt reduction in the kidney's ability to eliminate nitrogenous waste products and maintain fluid and electrolyte homeostasis.^{3,14} Despite the kidney's generous blood supply and large oxygen delivery, it remains at risk for ischemia in the perioperative period. The AKI may be classified by either the site of instigating pathology or the degree of injury sustained, as measured by changes in GFR and reduction in urine output. In light of the heterogeneous causes of AKI and the difficulty in comparing literature using disparate definitions,¹⁴ there has been a great deal of recent interest in standardizing and streamlining the classification of AKI.

Classification

The AKI has traditionally been classified by dividing the primary pathophysiology into prerenal, intrarenal, or postrenal causes ([Figure 16.11](#)).¹⁴

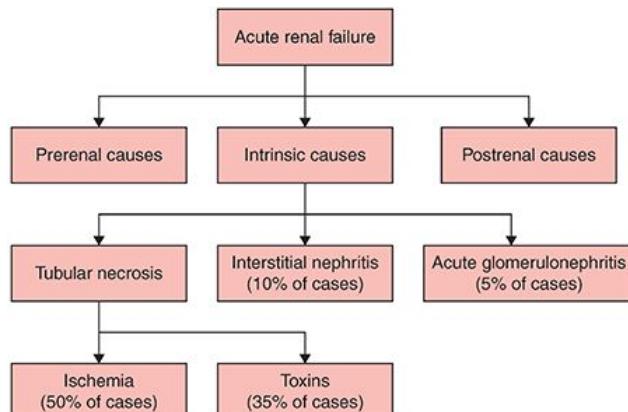


FIGURE 16.11 Classification of acute renal failure. From Thadhani R, Pascual M, Bonventre JV. Acute renal failure. N Engl J Med. 1996;334(22):1448-1460. Copyright © 1996 Massachusetts Medical Society.

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Prerenal Azotemia

The term **azotemia** refers to any condition characterized by abnormally high levels of nitrogen-containing compounds, such as urea, creatinine, and other nitrogen-rich compounds, in the blood. Prerenal azotemia refers to decreases in renal function due to hypoperfusion in the setting of intact glomeruli and tubules. Correcting the underlying problems in circulation will improve renal function. Common causes of prerenal azotemia in hospitalized patients include septic shock, heart failure, liver failure, and perioperative hemodynamic changes that lead to decreased renal perfusion.¹⁴ Medications may also be implicated in at-risk patients. Nonsteroidal anti-inflammatory drugs (NSAIDs) are known to precipitate prerenal azotemia in hypovolemic patients or in patients with congestive heart failure.¹⁵ Calcineurin inhibitors (eg, cyclosporine and tacrolimus) also reduce GFR and lead to prerenal azotemia by causing vasoconstriction of afferent renal arteries.^{15,16}

Intrinsic Causes of Acute Kidney Injury

The most common cause of intrinsic renal failure is acute tubular necrosis (ATN), caused by either ischemia or nephrotoxic agents. Less common causes seen perioperatively include acute glomerulonephritis and interstitial nephritis from such agents as β -lactam antibiotics and NSAIDs (see [Figure 16.11](#)).⁸ In cases of ATN secondary to ischemia, prolonged decreases in renal blood flow stimulate epithelial cells to reabsorb sodium to restore renal blood flow. This increase in active transport in the renal medullary tubules exacerbates the mismatch of oxygen supply and demand, leading to injury and the expression of proteins that regulate the response to hypoxia.^{17,18} Thus, prerenal azotemia leads to ATN, and both entities may be considered to be on the continuum of ischemic renal disease.

Renal tubule cells are particularly susceptible to ischemia because of their transport-related oxygen requirements and the low baseline blood flow to the renal medulla. Injury is worsened both by hypoxemia and by endothelial cell swelling, which further decreases perfusion. Nephrotoxic agents such as aminoglycosides and iodinated radiocontrast media may also lead to ATN, either by direct injury to tubules or by processes mediated by free radicals.^{14,19}

The ATN secondary to renal medullary ischemia is the most common perioperative cause of AKI. In this setting, adequate urine output may be falsely reassuring. Ischemic ATN leads to failure of the sodium-potassium ATPase pump in the renal tubules, impairing their ability to concentrate urine. Thus, urine output does not correspond to the degree of cell damage or GFR in patients exposed to trauma, shock, or cardiovascular surgery.²⁰

Postrenal Obstructive Nephropathy

Perioperative patients with AKI should also be evaluated for postrenal etiologies, particularly those with acute oliguria. Because the pathophysiology underlying this AKI involves hindrance to urine flow, this is also called **obstructive nephropathy**. Causes include renal stones, prostatic hypertrophy, and mechanical obstruction of urinary catheters.

Acute Kidney Injury Diagnosis

Diagnostic Criteria

As recently as 2004, there was no widespread consensus definition of acute renal failure (ARF). Comparison of the literature was challenging as definitions and categories varied between studies. In 2004, the Acute Dialysis Quality Initiative group conducted a systematic review and consensus conference, which produced a five-tiered classification scheme for ARF, called **RIFLE** (risk, injury, failure, loss of kidney function, and end-stage kidney disease) ([Figure 16.12](#)).²¹ This scheme is based on easily measurable clinical variables and includes in its definition an accommodation for acute or chronic kidney disease.

RIFLE criteria		
	GFR criteria	Urine output criteria
Risk	Increased SCr by 1.5× or GFR decrease by 25%	UO < 0.5 mL/kg/h for six hours
Injury	Increased SCr by 2× or GFR decrease by 50%	UO < 0.5 mL/kg/h for twelve hours
Failure	Increased SCr by 3× or GFR decrease by 75% or SCr > 4 mg/dL	UO < 0.3 mL/kg/h for 24 hours or Anuria for 12 hours
Loss	Persistent acute renal failure (four weeks duration)	
ESKD	End stage kidney disease (greater than three months)	

FIGURE 16.12 The RIFLE criteria. Abbreviations: ESKD, end-stage kidney disease; GFR, glomerular filtration rate; SCr, serum creatinine; UO, urine output. Adapted by permission from Springer: Bellomo R, Ronco C, Kellum JA, et al; Acute Dialysis Quality Initiative Workgroup. Acute renal failure—definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care. 2004;8(4):R204-R212.

The RIFLE classification includes three levels of renal dysfunction and two clinical outcomes. The degrees of renal dysfunction are defined either by changes in (1) SCr or estimated GFR or (2) oliguria. A patient may be categorized by meeting one criterion, the other, or both. The criterion that leads to the worst classification should be used.²¹

- R—risk of renal dysfunction: increased SCr by 1.5-fold (GFR decrease by 25%) or urine output less than 0.5 mL/kg per hour for 6 hours
- I—injury to the kidney: increased SCr by twofold (GFR decrease by 50%) or urine output less than 0.5 mL/kg per hour for 12 hours
- F—failure of kidney function: increased SCr by threefold (GFR decrease by 75%), SCr greater than 4 mg/dL, or urine output less than either 0.3 mL/kg per hour for 24 hours or anuria for 12 hours

Clinical outcomes include the following:

- L—Loss of kidney function is equivalent to persistent ARF, needing renal replacement therapy for more than 4 weeks.
- E—end-stage kidney disease: need for dialysis for more than 3 months

Proposed modifications to the RIFLE criteria were made by the Acute Kidney Injury Network (AKIN) in 2007 (Figure 16.13).²² The first three stages of RIFLE (risk, injury, and failure) correspond to the first three stages of injury in AKIN definitions. In addition, stage 1 AKI includes patients with a rise in SCr as little as 0.3 mg/dL, as even small increases in SCr are associated with worse outcomes.^{22,23} The AKIN further tightens the window to diagnosis of AKI by lab criteria or urine output to 48 hours as opposed to 7 days. Any patient with renal replacement therapy is included in stage 3, regardless of duration of therapy or concurrent urine output. Finally, “loss” and “end-stage kidney disease” have been removed, as they describe long-term outcomes rather than short-term categories. The RIFLE and AKIN definitions have been compared and are in general concordance. It has been suggested that the AKIN definitions do not provide significant advantages despite the increased sensitivity of stage 1 AKI.^{24,25}

RIFLE criteria			Acute Kidney Injury Network criteria		
	GFR criteria	Urine output criteria	Stage	Creatinine	Urine output criteria
Risk	Increased SCr by 1.5x or GFR decrease by 25%	UO < 0.5 mL/kg/h for six hours	1	1.5 to 2 times baseline or increase of 0.3 mg/dL	UO < 0.5 mL/kg/h for six hours
Injury	Increased SCr by 2x or GFR decrease by 50%	UO < 0.5 mL/kg/h for twelve hours	2	Increased 2 to 3 times baseline	UO < 0.5 mL/kg/h for twelve hours
Failure	Increased SCr by 3x or GFR decrease by 75% or SCr > 4 mg/dL	UO < 0.3 mL/kg/h for 24 hours or Anuria for 12 hours	3	>3 times baseline or SCr > 4.0 mg/dL with an acute increase of 0.5 mg/dL	UO < 0.3 mL/kg/h for 24 hours or Anuria for 12 hours
Loss	Persistent acute renal failure (four weeks duration)				
ESKD	End stage kidney disease (greater than three months)				

FIGURE 16.13 The RIFLE criteria compared to Acute Kidney Injury Network criteria. Abbreviations: ESKD, end-stage kidney disease; GFR, glomerular filtration rate; SCr, serum creatinine; UO, urine output. Adapted by permission from Springer: Mehta RL, Kellum JA, Shah SV, et al; Acute Kidney Injury Network. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care. 2007;11(2):R31.

In 2012, the Kidney Disease: Improving Global Outcomes (KDIGO) work group developed a classification meant to improve use in clinical practice. This classification scheme combines RIFLE and AKIN classifications (**Table 16.2**). In KDIGO classification, stage 1 AKI is defined as an increase in SCr of at least 0.3 mg/dL within 48 hours, or an increase in SCr to more than 1.5 times baseline, or a decrease in urine output to less than 0.5 mL/kg per hour for 6 hours.²⁶

TABLE 16.2		
Kidney Disease: Improving Global Outcomes classification of acute kidney injury		
Stage	SCr/GFR criteria	Urine output criteria
1	Increase SCr \geq 0.3 mg/dL or increase SCr \geq 1.5–2x	<0.5 mL/kg per hour for >6 hours
2	Increase SCr >2–3x	<0.5 mL/kg per hour for >12 hours
3	Increase SCr >3 or increase SCr \geq 4 mg/dL or initiation of renal replacement therapy	<0.3 mL/kg per hour for 24 hours or anuria for 12 hours, or GFR <35 mL/minute/1.73 m ²

Abbreviations: GFR, glomerular filtration rate; SCr, serum creatinine.

Recent studies have examined the differences in the classification schemes to assess their diagnostic and prognostic abilities in various context. Studies have shown similar incidence of AKI, regardless of classification scheme, in critically ill patients,²⁷ heart failure patients,²⁸ and cardiac surgical patients.²⁹ In patients with myocardial infarction, KDIGO may be superior to RIFLE in diagnosing AKI and predicting mortality.³⁰

Biomarkers

As discussed earlier, the SCr and urine output are the most widely used diagnostic criteria to detect AKI. The use of SCr to estimate the GFR assumes steady-state conditions: Production of creatinine is equal to its clearance. It is therefore problematic to use SCr to estimate GFR in dynamic settings. Simply put, the rise in SCr lags an acute reduction in GFR. Furthermore, because even small changes in the GFR have significant impact on mortality and hospital length of stay,²³ the need for early detection of AKI has led to the pursuit for biomarkers that may give real-time information. The ideal biomarker should be specific to AKI, allow for early diagnosis, identify the cause, and allow for characterization of degree of injury. The hope is that earlier detection of AKI could lead to therapeutic interventions that improve outcomes, and research in this area has been very active for some time.

Neutrophil gelatinase-associated lipocalin (NGAL) has been identified as an early marker of AKI.^{31–33} Its expression is induced in renal tubular cells following ischemia-reperfusion injury, and it can be measured

either in serum or urine soon after injury. Significant research has investigated this promising biomarker, although its clinical use has been slowed by conflicting reports on its predictive value. An early meta-analysis suggested that NGAL is a useful predictor of early AKI across an array of clinical settings.²⁵ When using standardized assays, a generally agreed upon cutoff upper value of 150 ng/mL may be suggestive of AKI. Despite questions regarding appropriate cutoff values and assay technique, more recent reviews have reaffirmed NGAL's use in both the prediction of the presence and severity of AKI after cardiac surgery and to predict delayed graft function after kidney transplantation.³⁴

Other biomarkers of AKI are under ongoing investigation.³⁵ Cystatin C, a cysteine proteinase inhibitor produced by all nucleated cells, is small in size and easily filtered in the glomerulus. Because it is metabolized in the proximal renal tubules, urinary concentrations are insignificant. Furthermore, its short half-life means serum levels will reflect GFR. Interleukin-18 is synthesized both in the proximal tubular cells and in cells that mediate inflammatory response. Elevated levels are seen in patients with ATN, although its role as a biomarker of AKI is confounded by evidence indicating it may represent more closely the presence of general inflammatory processes. Lastly, kidney injury molecule-1 is a membrane protein expressed in injured proximal tubular epithelial cells. Although associated with ATN, its predictive value is still being defined.³⁵ Because AKI is a complex clinical phenomenon, biomarkers may be most useful when combined as a panel that covers different phases of the injury pattern. This approach may yield better insight into mechanism, prediction, and treatment strategies. Further research will also determine whether interventions in early AKI will affect clinical outcomes.

Anesthesia and the Kidneys

An understanding of kidney function is important for the anesthesiologist, as fundamental concepts of perioperative management include the maintenance of normal circulating volume, the regulation of electrolytes and acid-base status, and the clearance of metabolites and drugs. The perioperative time period is unique in that multiple potential insults, often concurrent or in rapid succession, challenge the kidney's functional ability. Perioperative AKI has an estimated overall incidence of 1% and is associated with an increase in hospital costs, postoperative complications, and ultimately risk of mortality.³⁶

Anesthesia and Renal Blood Flow

Several perioperative factors affect renal blood flow either directly by hemodynamic effects or indirectly through actions of the sympathetic nervous system or AVP. Regardless of the immediate cause, a fall in renal blood flow tends to decrease the GFR by diminishing blood flow to the renal cortex. Likewise, decreased renal blood flow puts the renal medulla at risk for ischemia because the blood supply to this region is already low at baseline. The sum effect of these changes is conservation of sodium and water and, consequently, a decrease in urine output.

Many perioperative factors influence renal blood flow through changes in cardiac output or systemic arterial pressure. Anesthetic drugs commonly have significant direct hemodynamic effects, either by reducing systemic vascular resistance, depressing myocardial function, or decreasing effective preload. Likewise, perioperative hypovolemia (from preoperative fasting, bowel preparation, fluid shifts, acute hemorrhage, or any combination of factors) will decrease cardiac output and systemic arterial pressure, ultimately leading to a decrease in renal blood flow.

Because the kidney has rich autonomic innervation, renal blood flow is also highly sensitive to the action of the sympathetic nervous system. Sympathetic stimulation leads to increased renal vascular resistance, which has two significant effects. First, blood is shunted away from the kidneys to other organs, preserving perfusion of critical organs such as the brain and heart. Second, constriction of the afferent renal arterioles lowers glomerular capillary pressure and decreases the GFR. Whether the root cause is pain, surgical stimulation, or exogenous catecholamines, excessive sympathetic stimulation can decrease glomerular blood flow to the point that urine output drops to nearly zero. Furthermore, painful stimuli elicit the release of AVP, which increases water absorption from the collecting ducts, resulting in concentrated urine. Retention of sodium and water caused by positive end-expiratory pressure is not associated with changes in the circulating plasma concentrations of AVP.³⁷

These direct and indirect mechanisms altering renal blood flow are not mutually exclusive. A decrease in cardiac output will also lead to a release of AVP and an increase in the activity of the sympathetic nervous system and the RAAS. The AVP and aldosterone tend to restore both normal circulating volume and normal renal blood flow by retaining sodium and water. Hypovolemia from acute hemorrhage also increases sympathetic tone, further reducing renal blood flow.

The autoregulation of renal blood flow may also be affected by perioperative factors. Although most anesthetic drugs do not abolish autoregulation, it is impaired in the following circumstances: severe sepsis, acute kidney failure, and cardiopulmonary bypass (CPB). Sustained changes in mean arterial pressure (greater than 10 minutes) are associated with a decreased ability to autoregulate renal blood flow. Autoregulation of GFR, by contrast, is sustained over longer periods of time. Thus, the GFR may remain near-normal despite a marked reduction in renal blood flow.

It is important to remember that normal systemic arterial pressure does not ensure adequate renal blood flow and that renal ischemia may occur even in the absence of hypotension. Also, intraoperative urine output is a poor predictor of postoperative changes in renal function ([Figure 16.14](#)).³⁸ Hence, factors that commonly emerge in the perioperative setting including anesthetic agents, fluid shifts, stress response, changes in hemodynamics, and administration of catecholamines all have the potential to decrease renal blood flow and affect kidney function.

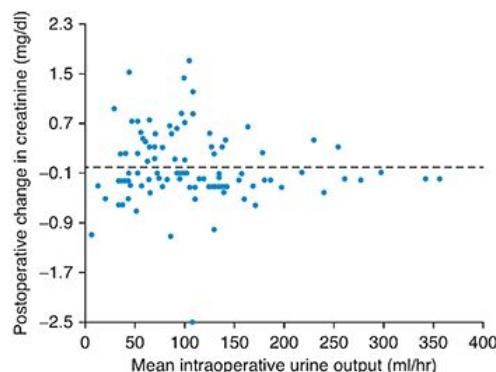


FIGURE 16.14 Intraoperative urine output. Mean intraoperative urine output does not correlate with postoperative changes in the plasma concentrations of creatinine. *From Alpert RA, Roizen MF, Hamilton WK, et al. Intraoperative urinary output does not predict postoperative renal function in patients undergoing abdominal aortic revascularization. Surgery. 1984;95:707-711. Reprinted with permission from Michael F. Roizen, MD.*

Perioperative Risk Assessment

An assessment of perioperative risk allows perioperative physicians to address this concern with patients and consultants as well as to plan the anesthetic with the aim of avoiding AKI. In the patient population undergoing general surgery, the risk of AKI is believed to be about 1%. Patient risk factors include age older than 56 years, male gender, active congestive heart failure, ascites, diabetes, and hypertension ([Table 16.3](#)).

TABLE 16.3

Risk factors for perioperative acute kidney injury	
Patient risk factors	Surgical risk factors
Age >56 years	Intraperitoneal surgery
Male gender	Emergent operation
Active congestive heart failure	
Ascites	
Diabetes	

Hypertension

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Special considerations should be taken in patients who are taking antihypertensives perioperatively, particularly angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and diuretics. Both ACEIs and ARBs inhibit the RAAS by decreasing the activity of angiotensin II, with ACEIs preventing the production of angiotensin II and ARBs preventing the binding of angiotensin II to its receptors. This results in vasodilation and in the perioperative setting can result in significant hypotension, potentially precipitating AKI. Additionally, when administered with NSAIDs, the concomitant vasoconstriction of the afferent arteriole caused by NSAIDs and vasodilation of the efferent arteriole caused by ACEIs can lead to significant renal dysfunction. Diuretics (ie, loop diuretics and thiazides) prevent the absorption of key electrolytes along different portions of the renal tubule, ultimately resulting in decreased water reabsorption and diuresis. Use of diuretics in the perioperative setting has the potential for causing significant dehydration and possible AKI and metabolic abnormalities.³⁹

Surgical factors associated with an increased likelihood of AKI include intraperitoneal surgery and emergent operations. Additional risk factors include requiring blood transfusions and sepsis.³⁶ The risk of perioperative AKI is of particular concern among patients undergoing cardiac surgery, vascular surgery, liver transplantation, or laparoscopic surgery.⁴⁰⁻⁴⁴

Cardiac Surgery

The rate of AKI in patients undergoing cardiac surgery ranges between 20% and 30%. Patients undergoing procedures that require CPB are at particular risk. Alterations in renal blood flow due to hypovolemia or direct sympathetic stimulation, hemolysis, inflammatory response, microemboli, and direct toxicity are several mechanisms for kidney injury in these patients. Furthermore, clamping or cannulation of the aorta in cardiac surgery is associated with atheromatous emboli to the kidneys.⁴⁵ Increased baseline SCr is the most significant risk factor for perioperative AKI after CPB. In patients with a baseline SCr between 2.0 and 4.0 mg/dL, the risk of AKI requiring dialysis is 10% to 20%. Other risk factors include ejection fraction less than 40% and preoperative use of an intra-aortic balloon pump.⁴⁶ Patients undergoing valve surgery are at higher risk than those undergoing coronary artery bypass grafting alone.⁴⁷

Vascular Surgery

The incidence of AKI among patients undergoing vascular surgery depends on the type of procedure being performed. Those undergoing open thoracic or abdominal aorta procedures have higher rates of AKI (26%-76%) when compared to their counterparts undergoing peripheral vascular operations (4%-19%). This patient population is at increased risk for AKI for many of the same reasons as patients undergoing cardiac surgery (eg, impaired renal blood flow, microemboli, and significant exposure to nephrotoxic contrast). Additionally, many of these patients have risk factors predisposing them to development of chronic kidney disease (ie, hypertension, diabetes, and hyperlipidemia).⁴⁸

Liver Transplantation

The risk of AKI in patients undergoing liver transplantation has been shown to be greater than 50%, and this injury has been associated with worse patient outcomes including decreased graft survival, prolonged intensive care unit length of stay, and overall mortality.⁴³ The increased rate of AKI in these patients is thought to be influenced by prolonged hypotension secondary to reperfusion and significant blood loss, increased risk of reoperation, and the use of nephrotoxic medications for immunosuppression. Patient-specific risk factors include severe preoperative liver disease (ie, decompensated cirrhosis), nonalcoholic steatohepatitis, female sex, poorly controlled diabetes, and obesity.^{43,49}

Laparoscopic Surgery

Insufflation of the abdomen with carbon dioxide during laparoscopic surgery increases in intra-abdominal pressure and activates the RAAS. These alterations have been shown to negatively impact renal blood flow and renal function.⁴⁴ However, the association between laparoscopy and an increased risk of perioperative AKI is inconsistent. Several case studies have reported the development of AKI after laparoscopic surgery⁵⁰⁻⁵²; however, there are relatively few large cohort studies that report on the overall rate of AKI after laparoscopic surgery. Reported rates of AKI following laparoscopic surgery have ranged between 5% to 35%.⁵³⁻⁵⁴ Moreover, there is data that suggest that laparoscopy is not associated with higher risk rates of AKI among patients undergoing major abdominal procedures.⁵⁵⁻⁵⁶ It is thought that the incidence and degree of kidney injury may relate to variations in the patients' volume status, positioning, insufflation pressure, and duration of pneumoperitoneum. Additional studies are needed to further clarify this relationship.

Intraoperative Management

Although the ability of the anesthesiologist to prevent AKI remains limited, general management principles include identifying potential causes of kidney injury (and mitigating their impact), minimizing exposure to nephrotoxic agents (NSAIDs and radiographic contrast), and maintaining renal blood flow. This can be accomplished by prompt correction of intravascular volume depletion and the maintenance of adequate systemic arterial pressure. Preoperative optimization of congestive heart failure, as well as maintaining normal cardiac output perioperatively, will help maintain renal blood flow. The judicious use of positive end-expiratory pressure and the avoidance of unnecessary increases in mean airway pressure will help maintain cardiac output and adequate renal blood flow. In laparoscopic surgery, using the lowest possible abdominal insufflation pressure and minimizing duration of insufflation will promote renal blood flow, although this must be balanced with operative needs. Adequate analgesia will minimize sympathetic nervous system-mediated decreases in renal blood flow. This may be a potential benefit of regional anesthesia. Agents used to promote afferent arteriolar dilation have not been shown to improve perioperative renal outcomes. Low-dose dopamine does not prevent AKI or improve mortality.⁵⁷ Fenoldopam mesylate, a selective dopamine agonist, may reduce the risk of AKI in selected patient populations,⁵⁸⁻⁵⁹ but further studies are needed to confirm this potential benefit.

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Intravenous Fluids and Electrolytes*

Updated by: Emily P. Wang • Jessica Spellman

Total body water and electrolytes are divided between the intracellular and extracellular compartments. The major electrolytes in the intracellular compartment are potassium, magnesium, calcium, and phosphate. The extracellular compartment consists of the interstitial, plasma, and transcellular fluid components, where sodium and chloride are the major electrolytes. Fluid movement between these spaces, and thus the effect of fluid therapies, depends on the levels of water, electrolytes, and colloid proteins among them and the composition and permeability of the membranes that separate them.

Total Body Fluid Composition

The adult body is composed of approximately 60% water, with some variation with age and gender as well as significant variation among different tissues. For example, muscle is about 75% water, whereas adipose tissue only 10%. About two-thirds of total body fluid is intracellular and one-third extracellular ([Figure 17.1](#)). The intracellular compartment is rich in potassium (the major cation), magnesium, calcium, phosphate (the major anion), and proteins. Extracellular volume (ECV) includes interstitial fluids (about 80% of the ECV), plasma (about 20%), and transcellular fluids, which are anatomically separate fluid spaces, such as the intraocular, gastrointestinal, and cerebrospinal fluids, and are not available for water and solute exchange with the remainder of the ECV. Extracellular fluids are rich in sodium (the major cation) and chloride (the major anion). These and other small ions move freely between plasma and interstitium in the extracellular compartment. The plasma also contains proteins, such as albumin and globulins, which create the colloid oncotic pressure. Plasma proteins are prevented from freely moving from vascular to interstitial space by the interplay of the vascular endothelial cells and the endothelial glycocalyx layer (EGL) coating the inside of the vascular space. Macromolecule movement out of the vascular space is dependent on the type of EGL pores and endothelial cell junctions, which have four phenotypes throughout the body. In the liver, spleen, and marrow, sinusoidal capillaries have large EGL pores and open fenestrations allowing macromolecules to pass between plasma and the interstitial space. The glomeruli have open capillary fenestrations with the effective pore size reduced by overlying EGL. Endocrine, choroid plexus, and gut mucosa vascular endothelial cells have inducible fenestrations. Nerve, muscle, connective tissue, and lung have nonfenestrated or continuous capillaries so that little transvascular filtration into the interstitium occurs in these tissues. In states of inflammation, changes in the endothelial cells and an increase in the number of large pores in the capillaries increase the amount of protein passing from vascular into interstitial spaces. The transcapillary escape rate of albumin to tissues is normally 5% per hour but can double during surgery and increase to 20% in sepsis.¹ Fluid in the interstitial space is returned to the circulation as lymph.² The cell membrane prevents sodium, the primary extracellular cation, from moving into the cell, except for a small amount by active pump transport, but isotonic fluids containing sodium added to the vascular space are distributed throughout the ECV so that only 20% of the volume infused remains in the plasma.³

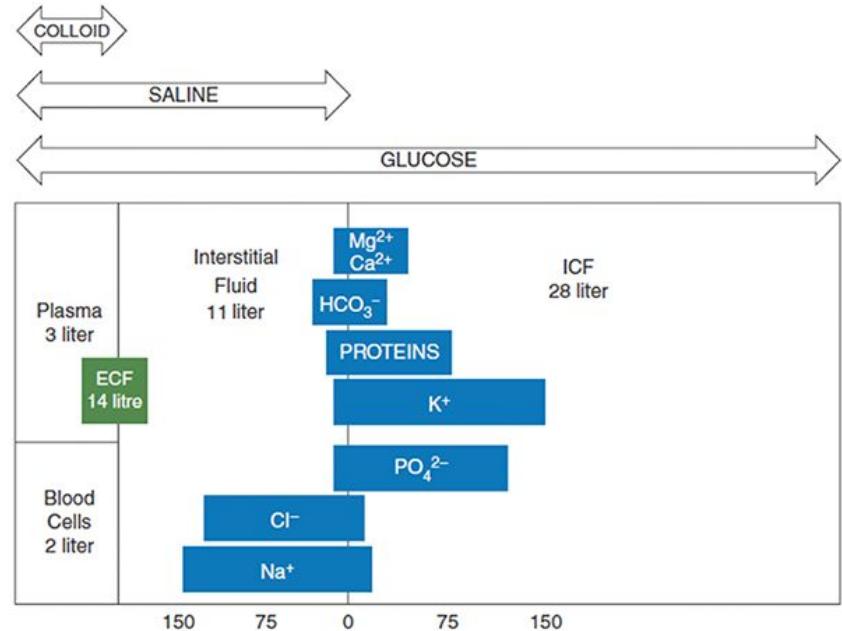


FIGURE 17.1 Body fluid compartments with main ion distribution. Abbreviations: ECF, extracellular fluid; ICF, intracellular fluid. Reprinted from Doherty M, Buggy DJ. Intraoperative fluids: how much is too much? Br J Anaesth. 2012;109(1):69-79. Copyright © 2012 Elsevier. With permission.

Intravenous Fluid Types

Crystalloids

Crystalloids are fluid solutions containing ion salts and other low-molecular-weight substances. Crystalloids can be categorized based on their tonicity or osmotic pressure of the solution with respect to that of plasma. Examples are listed in **Table 17.1**. Administering large volumes of normal saline (NS) can result in hyperchloremic metabolic acidosis.⁴ “Balanced” or “physiologic” crystalloid solutions contain a composition approximating that of extracellular fluid but are usually slightly hypotonic because of lower sodium concentration. Administering large volumes of balanced salt solutions can result in hyperlactatemia, metabolic alkalosis, and hypotonicity. Calcium-containing balanced salt solution may cause formation of microthrombi when infused with citrate-containing blood products.

TABLE 17.1

Common crystalloid solutions^a

Solution	Osmolarity (mOsm/L)	Tonicity	pH	Calories (kcal/L)	Na ⁺ (mEq/L)	Cl ⁻ (mEq/L)	K ⁺ (mEq/L)
NS	308	Iso	5		154	154	
D5NS	560	Hyper	4	170	154	154	
D5 1/2NS	406	Hyper	4	170	77	77	
LR	273	Iso	6.5	9	130	109	4
D5LR	525	Hyper	4.9	179	130	109	4
Plasma- Lyte	294	Iso	7.4	21	140	98	5
Solution	Ca ⁺⁺ (mEq/L)	Mg ⁺⁺ (mEq/L)	Glucose (g/L)	Lactate (mEq/L)	Acetate (mEq/L)	Gluconate (mEq/L)	

NS						
D5NS			50			
D5 1/2NS			50			
LR	3			28		
D5LR	3		50	28		
Plasma-Lyte		3			27	23

Abbreviations: D5LR, 5% dextrose in lactated Ringer; D5NS, 5% dextrose in normal saline; D5 1/2NS, 5% dextrose in 1/2 normal saline; LR, lactated Ringer; NS, normal saline.

^aData from Warren BB, Durieux ME. Hydroxyethyl starch: safe or not? *Anesth Analg*. 1997;84:206-212.

Perioperative fluid management is often discussed in the literature. Historically, fluid regimens were liberal, particularly for abdominal surgery, with patients receiving up to 7 L of intravenous (IV) hydration. Newer enhanced recovery after surgery pathways aim for a more restrictive IV fluid policy to promote faster recovery. Recently, the restrictive versus liberal fluid therapy in major abdominal surgery looked at disability-free survival up to 1 year after surgery in 3,000 patients receiving either liberal fluid management (10 mL/kg bolus at induction followed by 8 mL/kg per hour until the end of the surgery) or restrictive fluid management (5 mL/kg bolus at induction and 5 mL/kg per hour until the end of surgery). The study found no difference in the rate of disability-free survival at 1 year between the two groups ($P = .61$).⁵ Of the secondary outcomes, they found rate of acute kidney injury was higher in patients receiving restrictive fluid therapy ($P < .0001$). Current guidelines by the American Society of Anesthesiologists recommend a moderately liberal approach with overall positive fluid balance of 1 to 2 L at the end of surgery, with minimized preoperative fasting times and close consideration of hemodynamic monitoring to guide volume resuscitation.⁶

Furthermore, the best type of IV fluids used for fluid resuscitation is often debated. Recent studies have focused on comparing NS to balanced crystalloid solutions and their effects on the kidney and mortality. In a double-blind, cluster randomized, double-crossover trial of 2,278 patients in the intensive care unit (ICU) in New Zealand, patients received NS (0.9% sodium chloride) or a buffered crystalloid (Plasma-Lyte 148). The primary outcome was acute kidney injury based on five-category scoring system evaluating risk, injury, failure, loss, and end-stage renal failure criteria within 90 days after enrollment with secondary outcomes looking at incidence of renal replacement therapy (RRT) and in-hospital mortality. There was no significant difference between the two groups when assessing acute kidney injury ($P = .77$), the need for RRT ($P = .91$), or in-hospital deaths ($P = .4$).⁷ However, a newer study, the Isotonic Solutions and Major Adverse Renal Events Trial, looked at 15,802 critically ill adults using a cluster randomized, multiple-crossover, multicenter design and assigned patients to either receive saline or balanced crystalloids (lactated Ringer or Plasma-Lyte A). The primary outcome was major adverse kidney event, including death, initiation of RRT, or persistent renal dysfunction as defined as final creatinine value $\geq 200\%$ of baseline, within 30 days or hospital discharge. The balanced crystalloid group was found to have a decreased incidence of a major adverse kidney event as compared to the saline group ($P = .04$).⁸ In a related study, 13,347 noncritically ill patients in the emergency department were enrolled in a single-center, pragmatic, multiple-crossover trial comparing balanced crystalloids (lactated Ringer or Plasma-Lyte A) with saline. The primary outcome was hospital-free days, and secondary outcomes included major adverse kidney events as defined in the Isotonic Solutions and Major Adverse Renal Events Trial study. There was no difference between saline and balanced crystalloids in hospital-free days ($P = .41$); however, patients receiving balanced crystalloids had a lower incidence of death, requirement of new-onset RRT, and persistent renal dysfunction ($P = .01$). Thus, in critically ill patients and noncritically ill emergency department patients, treatment with balanced crystalloid solutions may offer the advantage of less adverse kidney events than treatment with NS.⁹

Colloids

Colloid solutions contain macromolecules suspended in electrolyte solutions. These macromolecules, such as plant or animal polysaccharides or polypeptides, remain in the plasma compartment longer than crystalloid solutions; however, their distribution has been shown to be context sensitive, with larger percentages of the

volume administered remaining intravascular in hypovolemic patients as compared to normovolemic patients.³ Semisynthetic colloid solutions are metabolized and excreted and thus have a shorter duration of effect than human albumin solutions.² Examples are listed in [Table 17.2](#).

TABLE 17.2

Common colloid solutions^a

Fluid	Trade Name	Source	Osmolarity (mOsm/L)	Na ⁺ (mmol/L)	Cl ⁻ (mmol/L)	K ⁺ (mmol/L)
Albumin 4%	Albumex	Human donor	250	148	128	
Albumin 5%		Human donor	309	154	154	
HES 10% (200/0.5)	Hemohes	Potato starch	308	154	154	
HES 6% (450/0.7)	Hextend	Maize starch	304	143	124	3
HES 6% (130/0.4)	Voluven	Maize starch	308	154	154	
HES 6% (130/0.4)	Volulyte	Maize starch	286	137	110	4
HES 6% (130/0.42)	Venofundin	Potato starch	308	154	154	
HES 6% (130/0.42)	Tetraspan	Potato starch	296	140	118	4
Fluid	Ca ⁺⁺ (mmol/L)	Mg ⁺⁺ (mmol/L)	Lactate (mmol/L)	Acetate (mmol/L)	Octonate (mmol/L)	Malate (mmol/L)
Albumin 4%					6.4	
Albumin 5%						
HES 10% (200/0.5)						
HES 6% (450/0.7)	5	0.9	28			
HES 6% (130/0.4)						
HES 6% (130/0.4)		1.5		34		
HES 6% (130/0.42)						
HES 6% (130/0.42)	2.5	1		24		5

Abbreviation: HES, hydroxyethyl starch.

^aData from Myburgh JA, Mythen MG. Resuscitation fluids. *N Engl J Med*. 2013;369:1243-1251.

Albumin (4%-5%)

Albumin solution is produced from human blood and suspended in saline. It is heat pasteurized at 60°C for 10 hours to reduce viral transmission. It is expensive to produce and distribute as compared to semisynthetic colloids and crystalloid solutions. The incidence of anaphylactoid reactions to albumin is 0.011%.¹⁰

The comparative effectiveness of fluid resuscitation with colloid versus crystalloid has been a long-standing controversy, which has been the subject of much recent clinical research. In the Saline versus Albumin Fluid Evaluation study, a multicenter, randomized, double-blind trial of 6,997 ICU patients, the effect of fluid resuscitation with albumin 4% or NS was evaluated. The primary outcome was death within 28 days. There was no significant increase in mortality ($P = .87$). The two groups also had similar rates of new single organ and multiple organ failure ($P = .85$), days spent in ICU ($P = .44$), days spent in hospital ($P = .3$), days of mechanical ventilation ($P = .74$), and days of RRT ($P = .41$).¹¹ In a post hoc analysis of the Saline versus Albumin Fluid Evaluation study of 460 patients with traumatic brain injury, the primary outcome of mortality was increased in the albumin-treated group (33.2%) versus the NS group (20.4%, $P = .03$).¹² In an additional subgroup analysis of 1,218 patients with severe sepsis, albumin administration was associated with a decreased risk of death as compared to NS with an adjusted odds ratio of 0.71 (95% confidence interval [CI], 0.52-0.97; $P = .03$).¹³ A more recent multicenter, open-label, randomized trial of 1,818 ICU patients with severe sepsis, the Albumin Italian Outcome Sepsis study, of 20% albumin and crystalloid versus crystalloid alone with primary outcome measure of death found no difference in survival at 28 or 90 days ($P = .29$).¹⁴ With many evaluations finding no significant clinical difference in ICU patients treated with albumin or saline, and increased mortality in the traumatic brain injury subset, providers must consider the costs of continuing to use such solutions.

Semisynthetic Colloid Solutions

Solutions include hydroxyethyl starch (HES) solutions, succinylated gelatin, urea-linked gelatin-polygeline preparations, and dextran solutions. The HES, the most commonly used semisynthetic colloid solutions, are created by attaching hydroxyethyl groups to carbons 2, 3, or 6 of the glucose moieties of starches of sorghum, maize, or potatoes. The HES solutions vary with respect to HES concentrations (6%-10%), molecular weights (70-670 kDa), molar substitution ratios (0.3-0.75), and crystalloid carrier solutions. The concentration influences the initial volume effect with 6% solutions being iso-oncotic and 10% solutions hyperoncotic. The HES is polydisperse with particles in a wide range of molecular mass (dispersity is a measure of the heterogeneity of sizes of molecules or particles in a mixture); thus, the molecular weight is averaged by either weight or number. The substitution ratio indicates the average fraction of glucose moieties bearing a hydroxyethyl group.¹⁵ The HES can also be named hexa- (0.6), penta- (0.5), or tetra- (0.4) starches for this level of substitution. Substitution increases the solubility of the starch in water and inhibits the destruction of the starch by amylase, thus prolonging intravascular retention. The HES can also be categorized with respect to the pattern of hydroxyethylation of the C₂ and C₆ carbon atoms. Hydroxyethyl groups in the C₂ position inhibit amylase access to the starch more effectively than hydroxyethyl groups at the C₆ position; thus, high C₂/C₆ ratios would be expected to hydrolyze more slowly. The maximum daily dose of HES is limited to 20 to 50 mL/kg of body weight per day but varies by solution.¹⁵

The HES is removed from the circulation by redistribution and renal excretion. Redistribution of HES results in temporary storage in the skin, liver, and kidneys. Skin deposition results in non-histamine-associated pruritus. After 24 hours, 23% of the total dose is interstitial, and at 26 weeks, trace amounts of HES are still detectable.¹¹ The HES molecules with greater molecular weights and increased substitution ratios tend to be stored more than those with more rapid clearance and deposition appears to be dose dependent.¹⁵

Renal excretion of HES occurs in two phases: immediate glomerular filtration of HES polymers less than 59 kDa and delayed glomerular filtration after HES metabolism by plasma α -amylase. This amylase functions as an endoamylase cleaving within the polyglucose chain instead of acting at the ends of the molecule, resulting in polydispersity and varying molecular weights of the remaining HES molecules in the plasma. Thus, pharmacokinetic parameters of plasma clearance and half-life will change over time, cannot be rigorously defined, and must not be interpreted as efficacy half-lives or contributing to the pharmacodynamics of volume effect of HES solutions.¹⁶ Additionally, the hydroxyethyl groups retard hydrolysis of the compound by amylases, allowing longer presence in the plasma. Plasma levels of amylase are elevated after HES administration for 72 hours, without evidence of increased pancreatic production, owing to decreased

renal elimination of amylase as it remains complexed to HES.¹⁰ The pharmacokinetic profile of some HES solutions after single dose and multiple infusions in healthy volunteers is described in [Tables 17.3](#) and [17.4](#),¹⁶ and in impaired renal function in [Table 17.5](#).¹⁷

TABLE 17.3

Pharmacokinetic parameters after a single dose of different hydroxyethyl starch types in healthy volunteers^a

HES type (concentration)	Dose (g)	C _{max} (mg/mL)	t _{1/2α} (hours)	t _{1/2β} (hours)	t _{1/2central} (hours)	AUC _∞ (mg · h/mL)	CL (mL per minute)	Infusion time (minutes)
670/0.75 (6%)	0.6/kg	13	6.3 ^b	46.4 ^c	NA	926.0	0.98	20 ^d
450/0.7 ^e (6%)	30	7.8	NA	300 ^f	NA	NA	NA	60
200/0.62 (6%)	30	5.2	5.08	69.7	44.42	NA	1.23	30
200/0.5 (10%)	50	8.0	3.35	30.6	7.12	NA	9.24	30
200/0.5 (6%)	30	6	NA	NA	NA	NA	4.88 ^g	15 ^h
200/0.5 (10%)	50	14	5.2	39.1	NA	NA	6.38 ^g	15 ^h
130/0.4 (6%)	26.3	3.7	1.39 ⁱ	12.1 ⁱ	1.55	14.3	31.4	30
130/0.4 (10%)	44.1	6.5	1.54 ⁱ	12.8 ⁱ	1.82	28.8	26.0	30

Abbreviations: AUC_∞, area under the plasma concentration-time curve from time zero to infinity; CL, total body clearance; C_{max}, maximum plasma concentration; HES, hydroxyethyl starch; NA, not available; t_{1/2α}, initial/distribution half-life; t_{1/2β}, terminal/elimination half-life; t_{1/2central}, elimination half-life from the central compartment.

^aReprinted by permission from Springer: Jungheinrich C, Neff TA. Pharmacokinetics of hydroxyethyl starch. *Clin Pharmacokinet*. 2005;44(7):681-699. Copyright © 2012 Springer Nature.

^bMean for 0-8 hours.

^cMean for 7-10 hours.

^dCalculated for 70 kg body weight.

^eProduct label declaration, however de facto similar to 670/0.75.

^fFor days 7-28 posttreatment.

^gMean for 0-24 hours.

^hBlood letting of 400 mL prior to infusion.

ⁱModel independent.

TABLE 17.4

Pharmacokinetic parameters and residual plasma concentrations after multiple infusions of different types of hydroxyethyl starch in healthy volunteers^a

HES type	Cumulative dose (g)	Treatment period	Plasma concentration 24 hours after last administration (mg/mL)	CL (mL per minute)	t _{1/2α} (hours)	t _{1/2β} (hours)	t _{1/2γ} (hours)	AUC (mg · h/mL)	
								Day 1	Last day ^b
450/0.7	90	3 days (3 × 30 g)	9.6	<1	NA	NA	NA	NA	>>day 1
200/0.62 ^c	150	5 days (5 × 30 g)	7.8	0.983 ^d	0.568	11.6	211	508	>>day 1
200/0.5 ^c	250	5 days (5 × 50 g)	3.4	4.86 ^d	0.389	6.98	113	171	>>day 1
200/0.5	250	5 days (5 × 50 g)	3.4	NA	NA	NA	NA	62.6	96.2
70/0.5	250	5 days (5 ×	3.0	NA	NA	NA	NA	NA	>>day

		50 g)							1
130/0.4	500	10 days (10 × 50 g)	<0.5	22.8 ^e	1.14 ^f	9.1 ^f	NA ^g	32.8	35.7

Abbreviations: AUC, area under the plasma concentration-time curve; CL, total body clearance; HES, hydroxyethyl starch; NA, not available; $t_{1/2\alpha}$, initial/distribution half-life; $t_{1/2\beta}$, terminal/elimination half-life; $t_{1/2\gamma}$, terminal/elimination half-life in a three-compartment model; >>, much greater than.

^aReprinted by permission from Springer: Jungheinrich C, Neff TA. Pharmacokinetics of hydroxyethyl starch. *Clin Pharmacokinet*. 2005;44(7):681-699. Copyright © 2012 Springer Nature.

^bDay 3, 5, or 10 according to length of treatment period.

^cThree-compartment modeling.

^dTaking days 1-5 into account.

^eDay 1: 23.7; day 10: 21.8.

^fMeans from days 1 and 10.

^gNot applicable for two-compartment modeling used; three-compartment modeling would yield a value of 33 h.

TABLE 17.5

Pharmacokinetic parameters after a single dose of hydroxyethyl starch 6% (130/0.4) 500 mL in different states of renal insufficiency^a

Variable	Renal group ^b	Mean (CV %) (geometric)	95% CI
AUC _(0-inf) (mg · h/mL)	15 to <30	41.1 (19.9)	(33.4, 50.6)
	30 to <50	35.1 (13.9)	(28.1, 43.8)
	50 to <80	20.0 (6.8)	(18.4, 21.8)
	80 to <120	25.5 (21.3)	(18.3, 35.4)
	All subjects	29.8 (34.4)	(25.3, 35.0)
C _{max} (mg/mL)	15 to <30	4.68 (17.4)	(3.90, 5.62)
	30 to <50	4.37 (14.1)	(3.50, 5.46)
	50 to <80	3.48 (12.5)	(2.99, 4.05)
	80 to <120	5.11 (25.4)	(3.45, 7.57)
	All subjects	4.34 (21.9)	(3.91, 4.81)
Total plasma clearance (L per hour)	15 to <30	0.73 (20.3)	(0.59, 0.90)
	30 to <50	0.85 (12.8)	(0.69, 1.05)
	50 to <80	1.52 (6.9)	(1.40, 1.65)
	80 to <120	1.19 (21.3)	(0.86, 1.65)
	All subjects	1.02 (34.9)	(0.87, 1.20)
Volume of distribution at steady state (L)	15 to <30	14.2 (18.4)	(11.7, 17.2)
	30 to <50	15.4 (12.7)	(12.7, 18.7)
	50 to <80	27.1 (6.6)	(24.9, 29.5)
	80 to <120	19.9 (23.1)	(13.8, 28.7)
	All subjects	18.4 (31.2)	(15.9, 21.3)
Terminal half-life (hours)	15 to <30	15.9 (8.8)	(14.5, 17.4)
	30 to <50	15.5 (9.6)	(13.3, 18.0)
	50 to <80	15.9 (5.4)	(14.8, 17.1)
	80 to <120	17.2 (6.8)	(15.4, 19.2)
	All subjects	16.1 (8.1)	(15.5, 16.7)

Abbreviations: AUC, area under the time concentration curve; CI, confidence interval; C_{max}, peak concentration; CV, coefficient of variation.

^aReprinted with permission from Jungheinrich C, Scharpf R, Wargenau M, et al. The pharmacokinetics and tolerability of an intravenous infusion of the new hydroxyethyl starch 130/0.4 (6%, 500 mL) in mild-to-severe renal impairment. *Anesth Analg*. 2002;95(3):544-551. Copyright © 2002 International Anesthesia Research Society.

^bDefined according to measurements of creatinine clearance (mL/min/1.73 m²).

The HES compounds have effects on coagulation with reductions in factor VIII, von Willebrand factor, and platelet function, although the exact mechanisms are unclear. Coagulation effects are noted even when used below recommended maximum doses. Solutions with more rapid degradation are associated with less effects on coagulation.¹⁵ The incidence of anaphylactoid reactions with HES use is 0.085%.¹¹

The HES solutions carry a US Food and Drug Administration black box warning with the following recommendations: Do not use HES solutions in critically ill adult patients including those with sepsis and those admitted to the ICU; avoid use in patients with preexisting renal dysfunction; discontinue use of HES at the first sign of renal injury; need for RRT has been reported up to 90 days after HES administration; continue to monitor renal function for at least 90 days in all patients; avoid use in patients undergoing open heart surgery in association with cardiopulmonary bypass due to excess bleeding; and discontinue use of HES at first sign of coagulopathy.¹⁸

The Crystalloid versus Hydroxyethyl Starch Trial evaluated HES versus NS in a multicenter, prospective, blinded, parallel-group, randomized controlled trial of over 7,000 adult ICU patients. Patients were randomized to receive either HES (6% [130/0.4] Voluven, Fresenius Kabi Norge AS, Halden, Norway) solution or NS until ICU discharge, death, or 90 days following randomization. The primary outcome was death 90 days after randomization, and secondary outcomes were acute kidney injury, failure, and treatment with RRT. There was no significant difference in mortality during the study period (18% in the HES group and 17% in the NS group, $P = .26$) or renal failure (HES group 10.4% and 9.2% NS group, $P = .12$); however, significant differences in renal injury (34.6% HES group and 38% NS group, $P = .005$) and RRT use (7% HES group, 5.8% NS group, $P = .04$) were found. Additionally, HES was associated with significantly more adverse events (0.3% vs 2.8%, $P < .001$).¹⁹

The HES (6% [130/0.42] Tetraspan, B. Braun Melsungen AG, Melsungen, Germany) has also been evaluated in a multicenter, parallel-group, blinded, randomized trial of 798 adult ICU patients with severe sepsis versus Ringer acetate in the Scandinavian Starch for Severe Sepsis/Septic Shock Trial. Primary outcomes measured were death or end-stage kidney failure at 90 days. Death was greater at 90 days in the HES group (51% vs 43%, $P = .03$). One patient in each group had end-stage kidney failure; however, in the 90-day period, 22% of HES patients were treated with RRT versus 16% in the Ringer acetate group ($P = .04$).²⁰

In the Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis multicenter, randomized trial evaluating adult ICU patients with severe sepsis, patients were randomized to receive either intensive insulin therapy or conventional insulin therapy in addition to either HES 10% pentastarch, HES 200/0.5, or lactated Ringer for fluid resuscitation. The primary end points were death and mean score for organ failure. There were 537 patients who were evaluated, and the trial was stopped early due to increased severe hypoglycemia events in the intensive insulin therapy group, but the comparison between HES and lactated Ringer was continued with all patients receiving conventional insulin therapy. The HES therapy was associated with higher rates of acute renal failure (34.9%, 22.8% in the lactated Ringer group, $P = .002$) and RRT than lactated Ringer (18.3%, 9.2% lactated Ringer group).²¹ Thus, use of HES is currently limited due to concerns for coagulopathy and impairment of renal function.

Assessing Fluid Responsiveness

Fluid responsiveness may be defined as a 15% increase in cardiac output following a 500-mL IV fluid bolus, indicating that the patient is still on the ascending limb of the cardiac output/end diastolic volume curve, also

referred to as the **cardiac function curve** ([Figure 17.2](#)).²² Fluid administration to a patient on the plateau part of the curve may be of little benefit and result in adverse effects. Filling pressure measures, particularly central venous pressure, correlate poorly with blood volume, and changes in central venous pressure have been shown to poorly predict hemodynamic response to fluid challenge.²³ Stroke volume changes due to increases or decreases in right ventricular preload may be used to assess fluid responsiveness. Positive pressure ventilation decreases right ventricular stroke volume by decreasing venous return to the right heart and increasing right ventricular afterload. The decrease in right ventricular stroke volume is passed on to the left ventricle over subsequent cardiac cycles, and if the left ventricle is preload dependent, decreases in the left ventricle stroke volume will cause a decrease in the arterial pulse pressure. These cyclic changes associated with positive airway pressure are greater when the ventricles are functioning on the steep, ascending portion of the cardiac function curve. Variation in the arterial pulse pressure can be derived from analysis of the arterial pressure waveform and variation greater than 12% to 13% is predictive of volume responsiveness.²⁴ Other measures of these positive pressure–associated stroke volume changes include systolic pressure variation of the arterial waveform, stroke volume variation derived from arterial pulse contour analysis, Pleth Variability Index derived from pulse oximeter waveform analysis, inferior vena cava diameter variation measured by echocardiography, and descending aortic blood velocity measured by esophageal Doppler. Measures dependent on variations caused by positive pressure ventilation are limited by the presence of arrhythmia, spontaneous breathing, tidal volume settings (8 mL/kg ideal body weight minimum required for pulse pressure variation and stroke volume variation),²⁴ low lung compliance (<30 mL/cm H₂O), increased abdominal pressure, and open chest surgery.²⁵

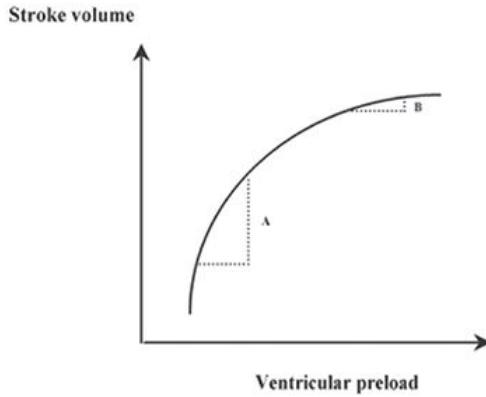


FIGURE 17.2 Schematic representation of Frank-Starling relationship between ventricular preload and stroke volume. A given change in preload induces a larger change in stroke volume when the ventricle operates on the ascending portion of the relationship (A, condition of preload dependence) than when it operates on the flat portion of the curve (B, condition of preload independence). *Reprinted by permission from Springer: Michard F, Teboul JL. Using heart-lung interactions to assess fluid responsiveness during mechanical ventilation. Crit Care. 2000;4(5):282-289. Copyright © 2000 Springer Nature.*

The end-expiratory occlusion test is useful in ventilated patients with cardiac arrhythmias, mild amplitude spontaneous breathing activity, or low tidal volume positive pressure ventilation. The test assesses the effect of a 15-second interruption in the ventilation on cardiac preload. A 5% increase in pulse contour cardiac output (sensitivity 91%, specificity 100%) or pulse pressure (sensitivity 87%, specificity 100%) is suggestive of volume responsiveness.²⁶ Passive leg raising maneuvers can be used to assess preload responsiveness in spontaneously breathing patients with arrhythmias but is limited in patients with intra-abdominal hypertension. The test is performed in a supine patient by elevating the legs to 45 degrees while assessing cardiac output or stroke volume over 30 to 90 seconds. Cardiac output measures during passive leg raising maneuvers are more accurate in predicting fluid responsiveness than arterial pressure measurements during the maneuver.²⁷

Important Fluid Constituents

Magnesium

Magnesium is almost all intracellular in bone (53%), muscle (27%), and soft tissues (19%), with less than 1% of total body magnesium in the extracellular fluid and only 0.3% in the plasma.²⁸ Most intracellular magnesium is bound to adenosine 5'-triphosphate and DNA, with less than 3% being in solution and ionized immediately available for intracellular magnesium homeostasis.²⁹ Plasma magnesium level is normally 1.7 to 2.4 mg/dL, where it is found in three states: ionized (62%), protein bound (33%), and complexed to anions (5%).²⁸ Given these distributions, plasma magnesium measurements may not be representative of total body magnesium stores. Also, magnesium measurements can be falsely elevated with hemolysis of the blood sample, which releases the intracellular electrolytes. Ingested magnesium is absorbed in the small intestines, primarily the ileum (75%),²⁹ via passive concentration effects and in the colon by active transcellular absorption.²⁵ Excretion occurs via the kidney with more than 95% of the filtered magnesium being reabsorbed in the renal tubules, with this mechanism effectively regulating the plasma level. Reabsorption occurs primarily (70%) in the ascending loop of Henle via passive mechanisms with a small amount occurring in both the proximal tubule via passive mechanisms and distal convoluted tubules via active mechanisms.²⁹ Bone, as the primary store of total body magnesium, provides a buffer for plasma magnesium levels through poorly understood mechanisms controlling magnesium incorporation into bone by osteoblasts and removal by osteoclasts.³⁰ Genetic mutations in colon transport channels³⁰ and loop of Henle junction proteins²⁹ can both result in hypomagnesemia.

Role of Magnesium

Magnesium plays a key role in many biologic processes including protein synthesis, neuromuscular function, and nucleic acid stability. It is involved in adenosine 5'-triphosphatase function, antagonizes *N*-methyl-D-aspartate (NMDA) glutamate receptors, inhibits catecholamine release, and is involved in the regulation of other electrolytes. For instance, magnesium antagonizes the uptake and distribution of calcium and modulates sodium and potassium currents through nicotinic acetylcholine receptors, NMDA receptors, and ion pumps, thus affecting membrane potentials. Magnesium has antiarrhythmic properties related to calcium channel antagonism.²⁹ The IV magnesium administration can exert muscle-relaxing effects, enhance nondepolarizing neuromuscular blockers, attenuate muscle fasciculations and potassium release with administration of succinylcholine, and precipitate skeletal muscle weakness in patients with Lambert-Eaton syndrome and myasthenia gravis. It has been used to reduce anesthetic requirements and attenuate cardiovascular effects of laryngoscopy and intubation. Magnesium has been shown to vasodilate blood vessels in many vascular beds (mesenteric, skeletal muscle, uterine, cerebral, coronary, and the aorta). It also decreases blood-brain barrier disruption and limits cerebral edema formation after brain injury.³¹ Side effects of IV administration include burning or pain on injection, drowsiness, nausea, headache, flushing, dizziness, muscle weakness, hypotension, and bradycardia.

Hypomagnesemia

Hypomagnesemia may result from dietary deficiency (as seen in chronic alcoholism), gastrointestinal malabsorption or secretion (diarrhea, vomiting, laxative use), renal losses (medication effects, nephrotoxic agents, endocrine disease, diabetic nephropathy), and chelation (citrate binding in the case of massive transfusion).²⁹ It is seen in as many as 11% of hospitalized patients and 65% of patients in the ICU. Clinical manifestations of hypomagnesemia result in cardiac and neuromuscular disorders and include symptoms of nausea, vomiting, weakness, convulsions, tetany, fasciculations, as well as electrocardiogram (ECG) abnormalities (prolonged PR and QT intervals, diminished T-wave morphology, torsades de pointes, and others) and accompanying hypokalemia and hypocalcemia.

Hypermagnesemia

Hypermagnesemia is rare and most commonly occurs with excessive administration of magnesium for therapeutic purposes. Clinical manifestations include QRS widening, hypotension, narcosis, diminution of deep tendon reflexes, respiratory depression from paralysis of muscles of ventilation, heart block, and cardiac arrest. Immediate treatment of life-threatening hypermagnesemia is with calcium gluconate, 10 to 15 mg/kg IV, followed by diuretics or dialysis, along with appropriate respiratory and circulatory support.

Preeclampsia

Magnesium appears to improve the clinical symptoms of preeclampsia by causing systemic, vertebral, and uterine vasodilation via direct effects on vessels as well as by increasing concentrations of endogenous vasodilators (endothelium-derived relaxing factor and calcitonin gene-related peptide) and attenuating endogenous vasoconstrictors (endothelin-1).³¹ Suggested dosing regimens of magnesium sulfate based on randomized trial data are 4 g IV loading dose over 10 to 15 minutes followed by infusion of 1 g per hour for 24 hours or 4 g IV loading dose with 10 g intramuscular (IM) followed by 5 g IM every 4 hours for 24 hours. Many other dosing regimens exist.³² Infusions or repeat dosing should be combined with clinical monitoring of urine output, respiratory rate, and deep tendon reflexes. Serum monitoring of magnesium levels should be performed for signs of toxicity or renal impairment. Magnesium crosses the placenta and may result in neonatal lethargy, hypotension, and respiratory depression if administered for prolonged duration (more than 48 hours).²⁹ In a Cochrane Summaries review, as compared to placebo or no anticonvulsant, magnesium was shown to decrease the risk of progression to eclampsia (relative risk [RR], 0.41; CI, 95%), decrease the risk of placental abruption (RR, 0.64; CI, 95%), and increase caesarean section (RR, 1.05; CI, 95%) but does not clearly affect maternal morbidity, stillbirth, or neonatal death or neurosensory disability at age 18 months.³² Reductions in maternal death were found to be nonsignificant.³³

Cardiac Dysrhythmias

Excess magnesium blocks myocardial calcium influx resulting in decreased sinus node activity, prolonged atrioventricular conduction time, and increased atrioventricular node refractoriness. Arrhythmias associated with hypomagnesemia are often³⁴ accompanied by hypokalemia. Normalization of both electrolytes is recommended.²⁸ Magnesium administration may decrease the incidence of severe arrhythmia after myocardial infarction, but use is limited by the incidence of hypotension.²⁹ There is no evidence that magnesium infusion during human cardiopulmonary resuscitation increases survival to hospital discharge; however, magnesium is recommended for patients with polymorphic wide complex tachycardia associated with familial or acquired long QT syndrome (torsades de pointes).³⁵ For digoxin-induced tachyarrhythmias in hypomagnesemic patients, magnesium should be administered while awaiting digoxin antibodies.²⁹ Prophylactic administration of magnesium during cardiopulmonary bypass has been shown to decrease the incidence of postoperative atrial fibrillation after coronary artery bypass surgery.³⁴

Analgesia

Magnesium has antinociceptive effects when administered IV or intrathecally, possibly due to inhibition of calcium influx, antagonism of NMDA receptors, or prevention of NMDA signaling. Data to support the use of magnesium as an analgesic or for preventative analgesia at this point is conflicting.²⁹

Asthma

Magnesium causes bronchodilatation via inhibition of calcium-mediated smooth muscle contraction, inhibition of histamine release from mast cells, and inhibition of nicotinic acetylcholine release. The IV magnesium (not inhaled) has been reported to improve bronchodilatation when standard therapies have failed; however, responses are variable.^{28,36}

Pheochromocytoma

Magnesium's arteriolar-dilating effects combined with reduction in catecholamine release may be beneficial in the management of patients with pheochromocytoma prior to tumor excision and in hemodynamic

catecholamine crisis.^{37,38}

Calcium

As an important component of the skeleton, there is more calcium in the body than any other mineral. The plasma concentration of calcium is maintained between 4.5 and 5.5 mEq/L (8.5 and 10.5 mg/dL) by an endocrine control system involving vitamin D, parathyroid hormone, and calcitonin, which regulate intestinal absorption, renal reabsorption, and bone turnover. Total plasma calcium consists of calcium bound to albumin and proteins (40%), calcium complexed with citrate and phosphorus ions (9%), and freely diffusible ionized calcium (51%).³⁹ It is the ionized fraction of calcium that produces physiologic effects and is normally 2 to 2.5 mEq/L. The ionized concentration of calcium depends on arterial pH, with acidosis increasing and alkalosis decreasing the concentration. Additionally, plasma albumin binds nonionized calcium; thus, in low albumin states, less nonionized calcium is protein bound making more available to return to storage sites, such as bone and teeth. This may decrease the total plasma calcium, but symptoms of hypocalcemia do not occur unless the ionized calcium concentration is also decreased. Thus, nonionized plasma calcium levels must be interpreted with knowledge of the plasma albumin concentration and can be corrected according to the following formula: corrected Ca^{++} (mg/dL) = measured Ca^{++} (mg/dL) + [0.8 × (4.0 – albumin (mg/dL)].⁴⁰ However, calculations to correct serum nonionized calcium for hypoalbuminemia may not be reliable in critically ill patients.⁴¹

Role of Calcium

The majority of total body calcium (>99%) is present in bone and provides the skeleton with strength and a reservoir to maintain the intracellular and extracellular calcium concentrations. Calcium is important for neuromuscular transmission, skeletal muscle contraction, cardiac muscle contractility, blood coagulation, and intracellular signaling in its function as a second messenger. In cardiac myocytes, calcium regulates contraction, relaxation, and electrical signals that determine rhythm and triggers hypertrophy via calcineurin mechanisms.⁴² In vascular smooth muscle, calcium induces a change in contractile state, increasing and decreasing vessel diameter.⁴³

Hypocalcemia

Hypocalcemia can result from decreased plasma concentration of albumin, hypoparathyroidism, acute pancreatitis, vitamin D deficiency, chronic renal failure associated with hyperphosphatemia, and citrate binding of calcium. This can result from transfused blood products, particularly fresh frozen plasma and platelets, also in hepatic failure and reduced citrate metabolism^{44,45} or use of citrate in dialysis or plasmapheresis,⁴⁶ sepsis, and critical illness.⁴⁶ Malabsorptive states rarely result in hypocalcemia as serum levels are maintained by bone calcium stores. Symptoms of hypocalcemia include neuromuscular excitability, including muscle twitching, spasms, tingling, numbness, carpopedal spasm, tetany, seizures, and cardiac dysrhythmias.⁴⁷ Calcium can be administered by oral or IV route. The IV preparations include calcium chloride which provides 27 mg of elemental calcium per milliliter and calcium gluconate, which provides 9 mg.⁴⁶ The IV calcium chloride may cause local irritation and necrosis if extravasated into the subcutaneous tissues and therefore is best administered centrally.

Hypercalcemia

Hyperparathyroidism is the most important cause of hypercalcemia and may be primary from parathyroid adenoma (85%), parathyroid hyperplasia (10%), which may be associated with multiple endocrine neoplasia syndromes, or, rarely (<1%), parathyroid carcinoma. Secondary hyperparathyroidism results from abnormal feedback loops present in renal failure and tertiary hyperparathyroidism from overactive responses to normal negative feedback mechanisms. Malignancies, such as squamous cell lung, breast, prostate, colon, adult T cell, and multiple myeloma, may result in release of parathyroid hormone-related peptide from tumor cells, resulting in inappropriate hypercalcemia.⁴⁶ Malignancy-related hypercalcemia may also result from osteolytic activity at sites of skeletal metastases commonly seen in breast cancer, multiple myeloma, and lymphoma,

and, rarely, malignancy-related hypercalcemia may result from tumor release of vitamin D.⁴⁰ Hypercalcemia may be associated with benign familial hypocalciuric hypercalcemia syndrome resulting from a mutation in calcium-sensing receptors. Hypercalcemia is also associated with granulomatous diseases such as sarcoidosis, tuberculosis, leprosy, coccidioidomycosis, and histoplasmosis and may result from excessive dietary supplement or medication side effects as a result of diuretic or lithium administration. Symptoms of hypercalcemia result from smooth muscle relaxation in the gut (constipation, anorexia, nausea, vomiting), decreased neuromuscular transmission (lethargy, hypotonia, confusion), renal effects (polyuria, dehydration, nephrolithiasis), and cardiac rhythm abnormalities (QTc shortening, J waves following QRS complex) as well as pancreatitis.⁴⁶

Treatment of hypercalcemia depends on the exact etiology but usually includes promoting renal excretion of calcium with IV fluids and loop diuretics while avoiding dehydration that would worsen any renal injury. Medications contributing to hypercalcemia should be discontinued and parathyroidectomy performed if indicated. Corticosteroids can be used to lower excessive calcium levels by inhibiting the effects of vitamin D, reducing intestinal absorption, and increasing renal excretion. Hydrocortisone 200 to 400 mg IV per day for 3 to 5 days⁴⁶ or prednisone 40 to 100 mg per day orally are recommended treatments for hypercalcemia associated with lymphoma and myeloma.⁴⁰ Bisphosphonates to inhibit osteoclast bone resorption may be useful: pamidronate 60 to 90 mg IV or zoledronate 4 mg IV. Gallium nitrate 100 to 200 mg/mL per day IV infusion for 5 days is used to inhibit osteoclastic bone resorption for paraneoplastic hypercalcemia refractory to bisphosphonate therapy.⁴⁰ Calcitonin 4 to 8 international units/kg subcutaneously or IM every 12 hours is less effective than bisphosphonates⁴⁰ or gallium nitrate⁴⁶ and works by inhibiting bone resorption and increasing renal calcium excretion. Mithramycin 25 µg/kg IV blocks bone resorption by inhibiting osteoclast RNA synthesis, but its use is limited by frequent dosing and toxicity (renal, hepatic, and hematologic).⁴⁰ Hemodialysis may also be used to treat acute, severe hypercalcemia.

Bone Composition

Bone is composed of an organic matrix that is strengthened by deposits of calcium salts. The organic matrix is greater than 90% collagen fibers, and the remainder is a homogeneous material called **ground substance**. Ground substance is composed of proteoglycans that include chondroitin sulfate and hyaluronic acid. Salts deposited in the organic matrix of bone are composed principally of calcium and phosphate ions in a combination known as **hydroxyapatites**.

The initial stage of bone production is the secretion by osteoclasts of collagen and ground substance. Calcium salts precipitate on the surfaces of collagen fibers, forming nidi that grow into hydroxyapatite crystals. Bone is continually being deposited by osteoblasts and is constantly being absorbed where osteoclasts are active. The bone-absorptive activity of osteoclasts is regulated by the parathyroid gland. Except in growing bones, the rate of bone deposition and absorption are equal, so the total mass of bone remains constant.

Because physical stress stimulates new bone formation, calcium is deposited by the osteoblasts in proportion to the compression load that the bone must carry. The deposition of bone at points of compression may be caused by small electrical currents induced by stress, called the **piezoelectric effect**, stimulating osteoblastic activity at the negative end of current flow. Osteoblasts are maximally activated at a bone fracture, the resulting bulge of osteoblastic tissue and new bone matrix being known as **callus**.

Osteoblasts secrete large amounts of alkaline phosphatase when they are actively depositing bone matrix. As a result, the rate of new bone formation is reflected by elevation of plasma concentration in alkaline phosphatase. Alkaline phosphatase concentrations are also increased by any disease process that causes destruction of bone (eg, metastatic cancer, osteomalacia, and rickets).

Calcium salts almost never precipitate in normal tissues other than bone. A notable exception, however, is atherosclerosis, in which calcium precipitates in the walls of large arteries. Calcium salts are also frequently deposited in degenerating tissues or in old blood clots.

Bisphosphonates

Bisphosphonates are drugs with a phosphorus-carbon-phosphorus (P-C-P) chemical structure that resemble inorganic pyrophosphate (**Figure 17.3**).⁴⁸ Inorganic pyrophosphate is involved in regulation of bone mineralization by binding hydroxyapatite crystals, inhibiting calcification. The phosphate groups of bisphosphonates, like inorganic pyrophosphate, bind hydroxyapatite crystals and become incorporated into sites of active bone remodeling, thus inhibiting calcification. The hydroxyl group attached to the central carbon further increases bisphosphonate's ability to bind calcium, and the final structural grouping is attached to the central carbon to determine the bisphosphonate's potency for inhibition of bone resorption. First-generation bisphosphonates (etidronate, clodronate, tiludronate), similar to inorganic pyrophosphate, become incorporated into adenosine triphosphate (ATP) by class II aminoacyl-transfer RNA synthetases after osteoclast-mediated uptake from bone and mineral surface. This abnormal ATP cannot be hydrolyzed, accumulates, and is believed to be cytotoxic to osteoclasts. Second- and third-generation bisphosphonates (alendronate, risedronate, ibandronate, pamidronate, and zoledronic acid) contain nitrogen or amino groups in this position, which increases the antiresorptive potency by binding and inhibiting farnesyl pyrophosphate synthase, leading to osteoclast apoptosis. Second- and third-generation bisphosphonate-induced osteoclast apoptosis can be detected by a reduction in biochemical markers of bone resorption; maximum suppression occurs within 3 months of initiation of oral therapy. Suppression is noted to be more rapid following IV administration. Duration of effect is a function of potency for mineral matrix binding, with zoledronic acid suppressing biochemical markers of bone resorption for up to 1 year in women with postmenopausal osteoporosis.

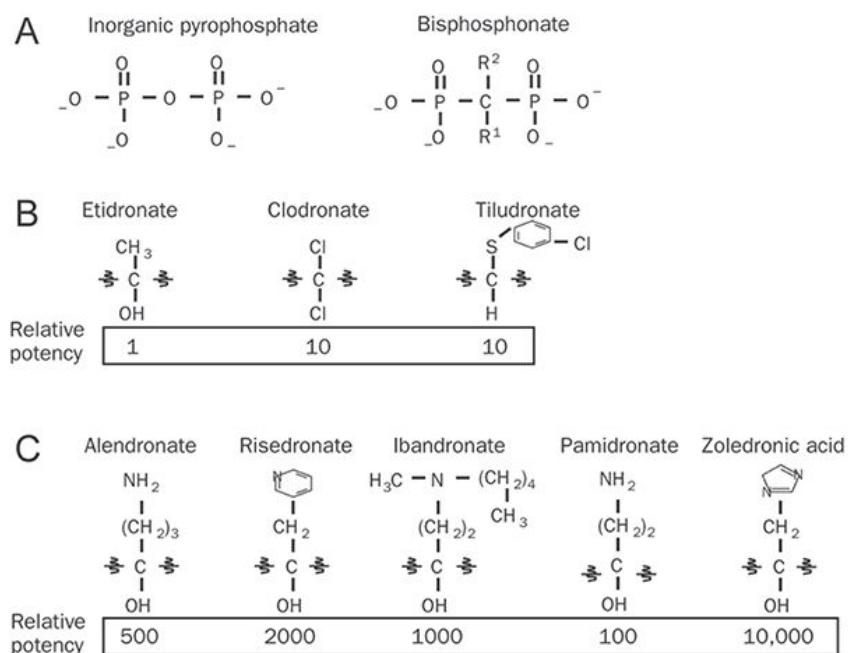


FIGURE 17.3 Inorganic pyrophosphate (PPi) and bisphosphonates. Reprinted from Drake MT, Clarke BL, Khosla S. Bisphosphonates: mechanism of action and role in clinical practice. Mayo Clin Proc. 2008;83(9):1032-1045. Copyright © 2008 Mayo Foundation for Medical Education and Research. With permission.

Clinical Uses

Bisphosphonates are useful in treating clinical conditions characterized by increased osteoclast-mediated bone resorption; for example, osteoporosis, Paget disease of bone, osteogenesis imperfecta, hypercalcemia, and malignant bony metastasis.

Pharmacokinetics

Oral bioavailability of bisphosphonates is low as they are hydrophilic with less than 1% absorbed after an oral dose. About 50% of the absorbed drug is retained in the skeleton, depending on renal function, rate of bone turnover, and binding site availability, and the remainder of drug is eliminated unchanged in the urine.^{48,49}

Side Effects

Hypocalcemia may follow IV bisphosphonate infusion; treatment is supportive with calcium and vitamin D supplementation. Ten percent to 42% of patients receiving nitrogen-containing bisphosphonates IV may experience an acute phase reaction⁴⁹ with fever, myalgias, arthralgias, headaches, and influenza-like symptoms. The incidence of this reaction decreases with each subsequent infusion; pretreatment with antihistamines and antipyretics⁴⁹ can reduce the incidence and severity of symptoms. Severe musculoskeletal pain may occur at any point after initiating bisphosphonates. Ocular inflammation (conjunctivitis, uveitis, episcleritis, scleritis) has been associated with both oral and IV bisphosphonate. Symptoms resolve within a few weeks of discontinuation. Esophageal irritation and erosion can occur with oral bisphosphonate therapy, particularly in the presence of gastroesophageal reflux disease or esophageal stricture; thus, it is often recommended that upright posture be maintained for 30 minutes after ingestion and that oral preparations be taken with a full glass of water.⁴⁹ Osteonecrosis of the jaw is associated with high-dose IV bisphosphonate use, primarily zoledronic acid and pamidronate, for oncologic conditions with an incidence of 1 to 10 per 100 patients. Associated risk factors for this complication include poor oral hygiene, history of recent dental procedures, denture use, and prolonged exposure to high IV bisphosphonate doses. The condition is rare for oral therapy of osteoporosis (1 in 10,000 to 1 in 100,000).^{48,49} Bisphosphonate dosing should be adjusted in patients with renal insufficiency, and its use is cautioned in patients with creatinine clearance less than 30 mL per minute because IV therapy may lead to rapid deterioration of renal function. Serious atrial fibrillation (life-threatening or resulting in hospitalization or disability) occurred more often in patients treated with zoledronic acid than placebo (1.3% vs 0.5%, $P < .001$) in the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly trial; however, there was no difference in the overall number of atrial fibrillation events in the two groups, and post hoc analysis of other trials has not yielded an association.⁴⁹ Hepatotoxicity has been reported with alendronate and zolendronate.⁴⁹

Denosumab

Denosumab is another antiresorptive therapy for metabolic bone diseases. It is a human monoclonal antibody against the receptor activator of NF- κ B ligand or RANKL. RANKL is required to differentiate and activate osteoclasts. Denosumab is reversible, administered biannually via subcutaneous route, and is not eliminated by the kidneys. Like the bisphosphonates, it is also associated with osteonecrosis of the jaw.⁵⁰

Potassium

Potassium is the second most common cation in the body and the principal intracellular cation. Approximately 3,500 mEq of potassium are present in the body of a 70-kg patient (40–50 mEq/kg). With 98% of the body's potassium being intracellular,⁵¹ the concentration in the extracellular fluid is about 4 mEq/L, and the intracellular concentration is 150 mEq/L. Because of this huge difference in concentration, estimation of total body potassium content from serum potassium values is inaccurate, even though the vast majority of potassium (>90%) is readily exchangeable between the intra- and extracellular compartments.

Role of Potassium

Potassium has an important influence on the control of osmotic pressure and is a catalyst of numerous enzymatic reactions. It is involved in the function of excitable cell membranes (nerves, skeletal muscles, cardiac muscle) and is directly involved in the function of the kidneys. In cardiac cells, potassium decreases action potential duration, electrical inhomogeneity, and risk of digoxin toxicity. Potassium is an endothelial-dependent vasodilator; it decreases vascular smooth muscle cell proliferation and inhibits thrombus formation and platelet activation.⁵¹ Disturbances of potassium homeostasis contribute to cardiac dysrhythmias, skeletal muscle weakness, and acid–base disturbances.

The kidney is the principal organ involved in body potassium homeostasis, primarily through control of active potassium secretion in the urine. This is different from most other electrolytes, which are regulated by control of reabsorption in the distal tubule. A number of hormones influence renal potassium secretion including aldosterone, glucocorticoids, catecholamines, and arginine vasopressin. Aldosterone acts at the renal collecting duct to increase reabsorption of sodium ions, which favors potassium secretion. Arginine vasopressin also increases secretion of potassium at the distal collecting tubule. Glucocorticoids influence renal potassium secretion by a direct action in the renal parenchyma. Catecholamines decrease renal secretion of potassium by an effect on the distal collecting system. Acidosis opposes and alkalosis favors potassium secretion. When uremia develops, gastrointestinal secretion of potassium increases, and when creatinine clearance is less than 20% of normal, gastrointestinal potassium loss can approach 20% of uptake.

Drugs Causing Hypokalemia

Diuretics that induce renal potassium loss are probably the most common cause of hypokalemia, but there are a number of other drugs that may result in this condition. Catecholamines shift potassium intracellularly, predominantly into the liver and skeletal muscle cells, and administration of β -adrenergic agonists in the treatment of bronchial asthma or premature labor may cause hypokalemia; in fact, β agonists may be useful in the treatment of hyperkalemia. Theophylline also causes potassium to move into cells, and hypokalemia should be anticipated in the presence of theophylline toxicity. Insulin induces potassium to move into cells and is used to treat severe hyperkalemia. Hypokalemia is caused by gastrointestinal losses of potassium from chronic laxative abuse or overaggressive bowel preparation for abdominal surgery. Large doses of penicillin and its synthetic derivatives increase excretion of potassium in the urine, and the direct nephrotoxicity of aminoglycoside antibiotics can also lead to excessive potassium loss.

Drugs Causing Hyperkalemia

Drugs that increase serum potassium concentrations do so by redistribution, suppression of aldosterone secretion, inhibition of potassium secretion in the distal collecting duct, or by direct cell destruction. Extracellular movement of potassium can result in plasma hyperkalemia without an increase in total body potassium. For example, succinylcholine causes a release of potassium from skeletal muscle cells, resulting in an increase of the serum potassium concentration by as much as 0.5 mEq/L. Digitalis toxicity can cause hyperkalemia by preventing potassium entry into cells. β -Adrenergic antagonists can cause a modest increase in the serum potassium concentration by virtue of an extracellular shift. Nonsteroidal antiinflammatory drugs may cause hyperkalemia by preventing aldosterone release. Potassium-sparing diuretics such as spironolactone inhibit the secretion of potassium in the distal collecting duct and can cause clinical hyperkalemia. Abrupt cell lysis from chemotherapy for acute blood cell proliferative malignancies can cause hyperkalemia through the release of intracellular potassium. Hyperkalemia can also occur with exogenous red blood cell transfusions as a result of lysed red blood cells resulting in higher levels of extracellular potassium.

Hypokalemia

Skeletal muscle weakness and a predisposition to cardiac dysrhythmias are the most prominent symptoms of clinically significant hypokalemia. At the cellular level, hypokalemia causes hyperpolarity, increases resting potential, hastens depolarization, and increases automaticity and excitability of cardiac cells,⁵² predisposing to tachydysrhythmias, including torsade de pointes⁵³ and atrial fibrillation,⁵² and sudden cardiac death particularly in the setting of acute myocardial infarction.⁵¹ Potassium depletion also produces diastolic dysfunction of the myocardium.⁵¹

Treatment

It is important to determine the cause of hypokalemia before aggressive potassium replacement is initiated. For example, if serum potassium concentrations are acutely decreased due to intracellular redistribution and potassium therapy is initiated, potentially serious hyperkalemia could occur. If total body depletion is the cause of hypokalemia, the amount of increase in the plasma concentration of potassium produced by supplementation may be small due to rapid redistribution into intracellular sites.

Life-threatening hypokalemia, presenting as malignant cardiac dysrhythmias, acute digitalis intoxication, or extreme neuromuscular collapse, requires supplemental IV potassium administration. The rate of potassium infusion depends on the urgency of the indication, with a common recommendation being administration of IV potassium no greater than 10 mEq per hour peripherally and 20 mEq per hour centrally in adults. Morbidity associated with supplemental potassium therapy is not trivial. Patients with diminished internal potassium regulation, especially diabetics and renal failure patients, are at risk for accidental treatment-induced hyperkalemia.

Hyperkalemia

The earliest sign of hyperkalemia is peaked T waves on ECG, which typically occurs when the serum potassium concentration reaches 6 mEq/L. As the extracellular concentration increases further, the transmembrane gradient is decreased, with prolongation of the P-R interval and QRS widening on the ECG. At this point, the risk of asystole or ventricular fibrillation due to cardiac conduction blockade increases dramatically. Asystole may also occur due to decreased automaticity in the sinoatrial node. Occasionally, hyperkalemia presents with neuromuscular symptoms such as paresthesias and skeletal muscle weakness.

Treatment

The decision to treat hyperkalemia, in contrast to hypokalemia, is based on the degree of increase in the serum potassium concentration and the symptoms and signs that are present. If ECG changes other than peaked T waves occur, or if the serum potassium concentration is greater than 6.5 mEq/L, the incidence of serious cardiac compromise is high and rapid intervention is indicated.

Calcium is administered to rapidly offset the adverse effects of potassium on cardiac conduction and contractility. Calcium activates calcium ion channels so that ion flux through these channels generates an action potential and restores myocardial contractility, effectively antagonizing the adverse cardiac effects of hyperkalemia. The IV administration of calcium must be slower in patients on digitalis preparations because acute hypercalcemia can precipitate digitalis toxicity. Serum potassium concentrations are not significantly changed by IV administration of calcium.

Other measures to treat hyperkalemia include IV administration of sodium bicarbonate, glucose-insulin mixtures, and β agonists to shift extracellular potassium ions into the cells. Alkalization of the blood with sodium bicarbonate, 0.5 to 1.0 mEq/kg IV, rapidly moves potassium into cells, decreasing the serum potassium level for as long as the arterial pH is increased. Glucose-insulin infusion (50 mL of 50% glucose plus 10 units of regular insulin) produces a sustained transfer of extracellular potassium into cells, resulting in a 1.5 to 2.5 mEq/L decrease in the serum potassium concentration after approximately 30 minutes. Sodium polystyrene sulfonate (Kayexalate) is an orally or rectally administered sodium exchange resin used to remove extracellular potassium in exchange for sodium in the large intestine. Potassium removal from the body also may be achieved by loop diuretics or, most rapidly and effectively, hemodialysis.

Phosphate

Phosphate is the major intracellular anion. The majority (85%) of total body phosphate is stored in the bone as hydroxyapatite crystals within the organic matrix. Most of the remainder is stored in soft tissue as phosphate, with only 1% located in the plasma.⁵⁴ The normal plasma concentration of phosphate is 3.0 to 4.5 mg/dL, accounting for both organic and inorganic forms.

Phosphate is important in energy metabolism, intracellular signaling (cyclic adenosine monophosphate and cyclic guanosine monophosphate), cell structure (phospholipids), oxygen delivery (2,3-disphosphoglycerate), regulation of the glycolytic pathway, the immune system, the coagulation cascade, and buffering to maintain normal acid-base balance. Phosphorus regulation is a result of the interplay of phosphate and calcium levels, vitamin D, and parathyroid hormone on gastrointestinal absorption, renal reabsorption, and bone storage. Phosphorous absorption from the gastrointestinal tract and reabsorption in the kidney proximal convoluted tubules is stimulated by vitamin D, and renal reabsorption of phosphorous is inhibited by the effects of parathyroid hormone. Renal disease disrupts this regulation, and ectopic tissue calcification as well as hyperphosphatemia may result.³⁹

A decrease in the plasma concentration of phosphate permits the presence of a higher plasma concentration of calcium and inhibits deposition of new bone salts. Hypophosphatemia (phosphorus concentration <1.5 mg/dL) causes a decrease in the concentration of ATP and 2,3-diphosphoglycerate in erythrocytes. Profound skeletal muscle weakness sufficient to contribute to hypoventilation may be caused by hypophosphatemia as well as central nervous system dysfunction and peripheral neuropathy. Causes of hypophosphatemia include alcohol abuse; prolonged parenteral nutrition; medications such as acetazolamide, catecholamines, and theophylline; paracetamol overdose; large burns; recovery from hypothermia; hemodialysis; salicylate poisoning; and gram-negative bacteremia.⁵⁴

Iron

Iron present in food is absorbed from the proximal small intestine, especially the duodenum, into the circulation, where it is bound to transferrin. Transferrin is a glycoprotein that delivers iron to specific receptors on cell membranes. Approximately 80% of the iron in plasma enters the bone marrow to be incorporated into new erythrocytes. In addition to bone marrow, iron is incorporated into reticuloendothelial cells of the liver and spleen. Iron is also an essential component of many enzymes necessary for energy transfer. A normal range for the plasma iron concentration is 50 to 150 µg/dL.

Iron that is stored in tissues is bound to protein as ferritin or in an aggregated form known as **hemosiderin**. Hemoglobin synthesis is the principal determinant of the plasma iron turnover rate. When blood loss occurs, hemoglobin concentration is maintained by mobilization of tissue iron stores. Indeed, hemoglobin concentrations become chronically decreased only after these iron reserves are depleted. For this reason, the presence of a normal hemoglobin concentration is not a sensitive indicator of tissue iron stores. The infant, parturient, and menstruating female may have iron requirements exceeding amounts available in the diet and develop iron-deficiency anemia. Absorption of iron from the gastrointestinal tract is increased by ascorbic acid (vitamin C) or in the presence of iron deficiency. Antacids bind iron and impair its systemic absorption.

Iron Deficiency

Iron deficiency is estimated to be present in 20% to 40% of menstruating females but only about 5% of adult males and postmenopausal females. Attempts to prevent this deficiency of iron in large parts of the population include the addition of iron to flour, use of iron-fortified formulas for infants, and the prescription of iron-containing vitamin supplements during pregnancy.

Causes

Causes of iron-deficiency anemia include inadequate dietary intake of iron, increased iron requirements due to pregnancy or blood loss, or interference with absorption from the gastrointestinal tract. Most nutritional iron deficiency in the United States is mild. Severe iron deficiency is usually the result of blood loss, either from the gastrointestinal tract or, in females, from the uterus. Partial gastrectomy,⁵⁵ malabsorptive bariatric surgery,⁵⁶ and sprue are causes of inadequate iron absorption.

Diagnosis

Iron deficiency initially results in a decrease in iron stores and a parallel decrease in the erythrocyte content of iron. Depleted iron stores are indicated by decreased plasma concentrations of ferritin and the absence of reticuloendothelial hemosiderin in a bone marrow aspirate. Plasma ferritin concentrations of less than 12 µg/dL are diagnostic of iron deficiency. Iron-deficiency anemia is defined as depletion of total body iron associated with a decreased red cell hemoglobin concentration. The large physiologic variation in hemoglobin concentration, however, makes it difficult to reliably identify all individuals with iron-deficiency anemia. Because iron-deficiency anemia is so common in infants, menstruating females, and recent parturients, mild anemia in these patients is typically treated empirically with iron supplementation before pursuing a more exhaustive diagnostic workup. However, in males and postmenopausal females, iron deficiency is much less common so it is important to search for a cause of blood loss whenever anemia is present.

Treatment

Prophylactic use of iron preparations should be reserved for individuals at high risk for developing iron deficiency, such as pregnant and lactating females, low-birth-weight infants, and females with heavy menses. The inappropriate prophylactic use of iron should be avoided in adults because excessive accumulation of iron may damage tissues.

In iron-deficiency anemia, administration of medicinal iron increases the rate of erythrocyte production, resulting in a rise in hemoglobin concentration within 72 hours. If the concentration deficit of hemoglobin before treatment is more than 3 g/dL, therapeutic doses of oral or parenteral iron should increase the hemoglobin about 0.2 g/dL per day. An increase of 2 g/dL or more in the plasma concentration of hemoglobin within 3 weeks is evidence of a positive response to iron. If this response to iron therapy is not seen, other causes of anemia should be considered, such as the chronic blood loss, infectious process, or impaired gastrointestinal iron absorption.

There is no justification for continuing iron therapy beyond 3 weeks if a favorable response has not occurred. If a response to iron therapy is demonstrated, the iron should be continued until the hemoglobin concentration is normal and continued for 4 to 6 more weeks to reestablish iron stores. Full replenishment of tissue iron stores requires several months of therapy.

Oral Iron

Ferrous sulfate administered orally is the most frequent choice for the treatment of iron-deficiency anemia and is available as syrup, pills, or tablets. Ferric salts are less efficiently absorbed than ferrous salts from the gastrointestinal tract. Although other salts of the ferrous form of iron are available, they offer little or no advantage over sulfate preparations. The usual therapeutic dose of iron for adults to treat iron-deficiency anemia is 2 to 3 mg/kg (200 mg daily) in three divided doses. Prophylaxis and treatment of mild nutritional iron deficiency can be achieved with modest dosages of iron, such as 15 to 30 mg daily.

Nausea and upper abdominal pain are the most frequent side effects of oral iron therapy, particularly if the dosage is greater than 200 mg daily. Hemochromatosis is unlikely to result from oral iron therapy that is administered to treat nutritional anemia. Fatal poisoning from overdose of iron is rare, but children 1 to 2 years of age are most vulnerable. Symptoms of severe iron poisoning may occur within 30 minutes as vomiting, abdominal pain, and diarrhea. In addition, there may be sedation, hyperventilation due to acidosis, and cardiovascular collapse. Hemorrhagic gastroenteritis and hepatic damage are often prominent at autopsy in fatal iron toxicity. If iron overdose is suspected, a plasma concentration of greater than 0.5 mg/dL confirms the presence of a life-threatening situation, which should be treated with deferoxamine.

Parenteral Iron

Parenteral iron acts similarly to oral iron but should be used only if patients cannot tolerate or do not respond to oral therapy. In addition, tissue iron stores may be restored more rapidly with parenteral iron than oral therapy. There is no evidence, however, that the increase in hemoglobin is more prompt with parenteral iron than with oral iron.

Iron dextran injection contains 50 mg/mL of iron and is available for IM or IV use. After absorption, the iron must be split from the glucose molecule of dextran to become available to tissues. The IM injection is painful, and there is concern about malignant changes at the injection site. For these reasons, IV administration of iron is preferred over IM injection. A dose of 500 mg of iron can be infused over 5 to 10 minutes.

The principal major adverse effect of parenteral iron therapy is the rare occurrence of a severe allergic reaction presumably due to the presence of dextran. Less severe reactions include headache, fever, generalized lymphadenopathy, and arthralgias. Hemosiderosis is more likely to occur with parenteral iron therapy because it bypasses gastrointestinal absorptive regulatory mechanisms.

Copper

Copper is present in ceruloplasmin and is a constituent of other enzymes, including dopamine β -hydroxylase and cytochrome C oxidase. It is bound to albumin and is an essential component of several proteins. Copper

is thought to act as a catalyst in the storage and release of iron from hemoglobin. It is believed to be essential for the formation of connective tissues, hematopoiesis, and function of the central nervous system. Copper deficiency is rare in the presence of an adequate diet. Supplements of copper should be given during prolonged hyperalimentation.

Zinc

Zinc is an enzymatic cofactor essential for cell growth and the synthesis of nucleic acid, carbohydrates, and proteins. Adequate zinc is provided by a diet containing sufficient animal protein. Diets in which protein is obtained primarily from vegetable sources may not supply adequate zinc. Zinc deficiency may occur in elderly or debilitated patients or during periods of increased requirements as in growing children, pregnancy, lactation, or infection. Severe zinc deficiency occurs most often in the presence of malabsorption syndromes. Symptoms of zinc deficiency include disturbances in taste and smell, suboptimal growth in children, hepatosplenomegaly, alopecia, cutaneous rashes, glossitis, and stomatitis.

Chromium

Chromium is important in a cofactor complex with insulin and thus is involved in normal glucose utilization. Deficiency has been accompanied by a diabetes-like syndrome, peripheral neuropathy, and encephalopathy.

Selenium

Selenium is a constituent of several metabolically important enzymes. A selenium-dependent glutathione peroxidase is present in human erythrocytes. There seems to be a close relationship between vitamin E and selenium. Deficiency of selenium has been associated with cardiomyopathy, suggesting the need to add this trace element to supplements administered during prolonged hyperalimentation.

Manganese

Manganese is concentrated in mitochondria, especially in the liver, pancreas, kidneys, and pituitary. It influences the synthesis of mucopolysaccharides, stimulates hepatic synthesis of cholesterol and fatty acids, and is a cofactor in many enzymes. Deficiency is unknown clinically, but supplementation is recommended during prolonged hyperalimentation.

Molybdenum

Molybdenum is an essential constituent of many enzymes. It is well absorbed from the gastrointestinal tract and is present in bones, liver, and kidneys. Deficiency is rare, whereas excessive ingestion has been associated with a gout-like syndrome.

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Sympathomimetic Drugs*

Updated by: Javier Lorenzo

Naturally Occurring Catecholamines

Naturally occurring catecholamines are epinephrine, norepinephrine, and dopamine ([Table 18.1](#) and [Figure 18.1](#)).

TABLE 18.1

Classification and comparative pharmacology of sympathomimetics

	Receptors stimulated			Mechanism of action	Cardiac effects		
	α	β ₁	β ₂		Cardiac output	Heart rate	Dysrhythmias
Natural catecholamines							
Epinephrine	+	++	++	Direct	++	++	+++
Norepinephrine	+++	++	+	Direct	-	-	+
Dopamine	++	++	+	Direct	+++	+	+
Synthetic catecholamines							
Isoproterenol	0	+++	+++	Direct	+++	+++	+++
Dobutamine	0	+++	+	Direct	+++	+	±
Synthetic noncatecholamines							
Ephedrine	++	+	+	Direct and indirect	++	++	++
Phenylephrine	+++	0	+	Direct	-	-	NC
	Peripheral vascular resistance	Renal blood flow	Mean arterial pressure	Airway resistance	Central nervous system stimulation	Single intravenous dose (70-kg adult)	Continuous infusion dose (70-kg adult)
Natural catecholamines							
Epinephrine	±	--	+	--	Yes	2-10 mcg	1-35 mcg/min
Norepinephrine	+++	---	+++	NC	No	Not used	2-35 mcg/min
Dopamine	+	+++	+	NC	No	Not Used	2-20 µg/kg/minute
Synthetic catecholamines							
Isoproterenol	--	-	±	----	Yes	1-4 µg	1-5 µg/minute
Dobutamine	NC	++	+	NC		Not used	2-10 µg/kg/minute
Synthetic noncatecholamines							
Ephedrine	+	--	++	--	Yes	10-25 µg	Not used
Phenylephrine	+++	---	+++	NC	No	50-100 µg	20-300 mcg/min

Abbreviations: 0, none; ±, variable response; +, minimal increase; ++, moderate increase; +++, marked increase; -, minimal decrease; --, moderate decrease; ---, marked decrease; NC, no change.

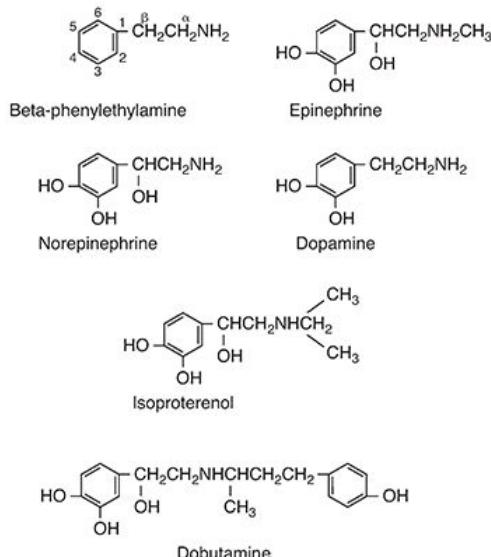


FIGURE 18.1 Sympathomimetics are derived from β -phenylethylamine, with a catecholamine being any compound that has hydroxyl groups on the 3 and 4 carbon positions of the benzene ring. The naturally occurring catecholamines are epinephrine, norepinephrine, and dopamine. Isoproterenol and dobutamine are synthetic catecholamines.

Epinephrine

Epinephrine is the prototype sympathomimetic. It is a circulating hormone synthesized, stored, and released from the adrenal medulla. Its natural functions upon release into the circulation include regulation of myocardial contractility, heart rate, vascular and bronchial smooth muscle tone, glandular secretions, and metabolic processes such as glycogenolysis and lipolysis. It is a potent activator of α -adrenergic receptors and also activates β_1 and β_2 receptors. Oral administration is not effective as epinephrine is rapidly metabolized in the gastrointestinal mucosa and liver. Therefore, epinephrine is administered subcutaneously, intravenously, or intramuscularly. Absorption after subcutaneous injection is slow because of local epinephrine-induced vasoconstriction. Epinephrine is poorly lipid soluble, preventing its entrance into the central nervous system (CNS) and accounting for the lack of cerebral effects. In cases of limited intravenous (IV) access such as in neonatal resuscitation, epinephrine can be administered via endotracheal tube.¹

Clinical Uses

As an agonist for all adrenergic receptors, epinephrine is an ideal agent for the treatment of life-threatening allergic reactions/anaphylaxis, of severe asthma and bronchospasm, and during cardiopulmonary resuscitation.² During periods of hemodynamic instability, it promotes myocardial contractility and increases vascular resistance. It also promotes inotropy during weaning from cardiopulmonary bypass. The Surviving Sepsis guidelines continue to support the use of epinephrine, either as a single agent or in combination with norepinephrine, to maintain adequate blood pressure in sepsis.^{3–5} Lastly, epinephrine is added to local anesthetic solutions to decrease systemic absorption prolonging the duration of action of the anesthetic for regional and local anesthesia. Epinephrine is used in local and field blocks to promote a bloodless surgical field.

Cardiovascular Effects

The cardiovascular effects of epinephrine result from stimulation of α - and β -adrenergic receptors (see **Table 18.1**).⁴ Stimulation of α_1 receptors leads to arteriolar vasoconstriction and pulmonary artery vasoconstriction. The α_1 receptors are predominantly located in cutaneous, splanchnic, and renal vascular beds. The β_2 receptor stimulation leads to vasodilation, predominantly in the skeletal muscles. The relative balance of α_1

and β_2 receptors in the vasculature of an organ determines epinephrine's overall effect on blood flow to the organ. In general, beta receptors are more sensitive to lower epinephrine doses, whereas effects on alpha receptors predominate at higher doses. Initial tachycardia may be followed by heart rate decreases due to baroreceptor reflexes. Venous return is also enhanced by vasoconstriction from the high density of alpha receptors in the venous vasculature system. Blood pressure is increased by an increase in cardiac index as well as an increase in systemic vascular resistance.

Epinephrine stimulates β_1 receptors causing an increase in heart rate, myocardial contractility, and cardiac output. The net effect of these systemic blood pressure changes is an increase in pulse pressure and a mild change in mean arterial pressure.

Epinephrine increases heart rate by accelerating the rate of spontaneous phase 4 depolarization, which also increases the likelihood of cardiac dysrhythmias. Epinephrine increases conduction velocity and decreases the refractory period in the atrioventricular node, bundle of His, Purkinje fibers, and ventricular muscle. It also may increase automaticity of latent pacemakers. Tachycardia, premature ventricular contraction, ventricular tachycardia, and ventricular fibrillation all may occur.

Increased cardiac output reflects epinephrine-induced increases in heart rate, myocardial contractility, and venous return. Repeated doses of epinephrine produce similar cardiovascular effects in contrast to the tachyphylaxis that accompanies administration of synthetic noncatecholamines that cause the release of norepinephrine, such as ephedrine. Myocardial oxygen consumption is increased with enhanced left ventricular preload, increased contractility, increased afterload, and tachycardia. Diastolic function is improved by increasing the rate of myocardial relaxation, and early left ventricular filling is enhanced. Epinephrine stimulates renal β receptors, resulting in increased secretion of renin. In usual therapeutic doses, epinephrine has no significant vasoconstrictive effect on cerebral arterioles. Coronary blood flow is enhanced by epinephrine,⁶ even at doses that do not alter systemic blood pressure.

The hemodynamic effects of epinephrine are attenuated and can be blocked by prior administration of α - or β -adrenergic receptor antagonists.⁴ Supratherapeutic doses of epinephrine may lead to acute heart failure, pulmonary edema, arrhythmias, hypertension, and myocardial ischemia.

Airway Smooth Muscle

Smooth muscles of the bronchi are relaxed by epinephrine-induced activation of β_2 receptors. By increasing intracellular concentrations of cyclic adenosine monophosphate (cAMP), β_2 stimulation decreases release of vasoactive mediators associated with symptoms of bronchial asthma. The bronchodilating effects of epinephrine are not seen in the presence of β -adrenergic blockade. In the presence of β -adrenergic blockade, epinephrine instead induces bronchoconstriction from stimulation of bronchial α receptors.

Metabolic Effects

Epinephrine has the most significant effect on metabolism of all the catecholamines.⁷ β_1 Receptor stimulation increases liver glycogenolysis and adipose tissue lipolysis, whereas α_1 receptor stimulation inhibits release of insulin. Liver glycogenolysis results from activation of hepatic phosphorylase enzyme. Lipolysis is due to epinephrine-induced activation of triglyceride lipase, which accelerates the breakdown of triglycerides to form free fatty acids and glycerol. Infusions of epinephrine usually increase plasma concentrations of glucose, cholesterol, phospholipids, and low-density lipoproteins. Release of endogenous epinephrine and the resulting glycogenolysis and inhibition of insulin secretion is the most likely explanation for perioperative hyperglycemia. In addition, epinephrine can inhibit peripheral glucose uptake, which is also due in part to inhibition of insulin secretion.

A multicenter, randomized, controlled, double-blind study of 330 patients with septic shock showed no difference in the duration of vasopressor use, intensive care unit or hospital length of stay, or 28- and 90-day mortality when vasopressor therapy with epinephrine plus placebo was compared with combined norepinephrine and dobutamine; however, the epinephrine group did have significantly lower arterial pH values over the first 4 days, with significantly higher arterial lactate values on day 1.⁸ Increased plasma concentrations of lactate presumably reflect epinephrine-induced glycogenolysis in skeletal muscles. Some

studies demonstrate that epinephrine-induced hyperlactatemia is primarily a transient phenomenon associated with inhibition of pyruvate dehydrogenase and has no relationship with cellular hypoxia and tissue perfusion or associated metabolic acidosis.⁹

Electrolytes

Selective β_2 -adrenergic agonist effects of epinephrine are speculated to reflect activation of the sodium-potassium pump in skeletal muscles, leading to a transfer of potassium ions into cells (Figure 18.2).⁹ The observation that serum potassium measurements in blood samples obtained immediately before induction of anesthesia are lower than measurements 1 to 3 days preoperatively is presumed to reflect stress-induced release of epinephrine (Figure 18.3).¹⁰ The ability of a nonselective β_1 and β_2 antagonist (propranolol) but not a cardioselective β_1 antagonist (atenolol) to prevent “preoperative hypokalemia” is consistent for a β_2 -adrenergic agonist effect as the explanation for potassium transfer (Figure 18.4).¹¹ In making therapeutic decisions based on a preinduction serum potassium measurement, especially in patients without a reason to experience hypokalemia, one should consider the possible role of preoperative anxiety and the release of epinephrine.

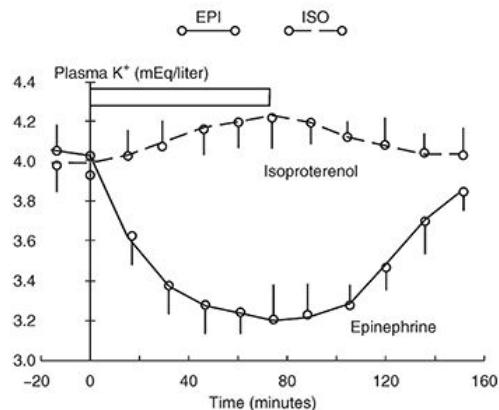


FIGURE 18.2 Selective β_2 -adrenergic agonist effects of epinephrine are responsible for stimulating the movement of potassium ions (K^+) into cells, with a resulting decrease in the serum potassium concentration. From Brown MJ, Brown DC, Murphy MB. Hypokalemia from beta₂-receptor stimulation by circulating epinephrine. N Engl J Med. 1983;309(23):1414-1419. Copyright © 1983 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

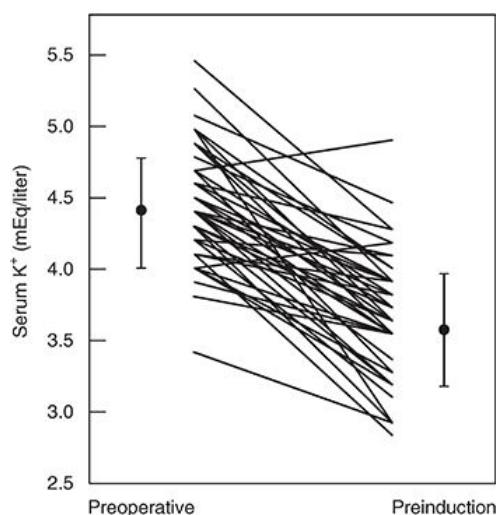


FIGURE 18.3 Individual and mean (\pm standard deviation) plasma potassium concentrations determined 1 to 3 days preoperatively and immediately before the induction (preinduction) of anesthesia. Reprinted with permission from Kharasch ED, Bowdle TA. Hypokalemia before induction of anesthesia and prevention by beta 2 adrenoceptor antagonism. *Anesth Analg.* 1991;72(2):216-220. Copyright © 1991 International Anesthesia Research Society.

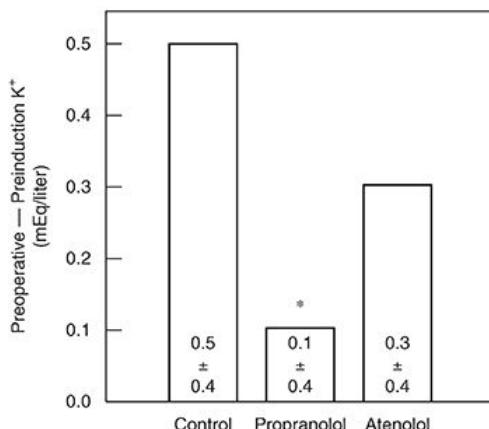


FIGURE 18.4 Propranolol, but not atenolol, was effective in blunting the difference between preoperative and preinduction serum potassium (K^+) concentrations compared with patients (controls) not receiving a β antagonist. Data are mean \pm standard deviation. The asterisk denotes a significant difference ($P < .02$) between controls and patients treated with propranolol. Reprinted with permission from Kharasch ED, Bowdle TA. Hypokalemia before induction of anesthesia and prevention by beta 2 adrenoceptor antagonism. *Anesth Analg.* 1991;72(2):216-220. Copyright © 1991 International Anesthesia Research Society.

Epinephrine-induced hypokalemia may contribute to cardiac dysrhythmias, which occasionally accompany stimulation of the sympathetic nervous system. Conversely, epinephrine may stimulate the release of potassium from the liver, tending to offset the decrease in extracellular concentration of this ion produced by entrance into skeletal muscles.

Ocular Effects

Epinephrine causes contraction of the radial muscles of the iris, producing mydriasis (dilation of the pupil). Contraction of the orbital muscles produces an appearance of exophthalmos.

Gastrointestinal and Genitourinary Effects

Epinephrine, norepinephrine, and isoproterenol produce relaxation of gastrointestinal smooth muscle. Activation of β -adrenergic receptors relaxes the detrusor muscle of the bladder, whereas activation of α -adrenergic receptors contracts the trigone and sphincter muscles.

Hepatosplanchnic vasoconstriction occurs as well as impaired renal blood flow as cardiac output is diverted to the dilated skeletal muscle vasculature.¹² This results in decreased hepatosplanchnic oxygen exchange and lactate clearance. The impairment of splanchnic circulation that occurs is greater than that associated with norepinephrine or dopamine.^{13,14} It may be dependent on the severity of the shock state and the dose of epinephrine used.

Norepinephrine

Norepinephrine is the endogenous neurotransmitter synthesized and stored in postganglionic sympathetic nerve endings and released with sympathetic nerve stimulation. It is a hydroxylated derivative of dopamine and the immediate precursor of epinephrine. Norepinephrine stimulates β_1 - and α_1 -adrenergic receptors. It is

approximately equal in potency to epinephrine for stimulation of β_1 receptors but, unlike epinephrine, has minimal effect at β_2 receptors (see [Table 18.1](#)).

Through its action on β_1 receptors, norepinephrine increases heart rate, conduction, and contractility. Norepinephrine is a potent α_1 agonist producing intense arterial and venous vasoconstriction in all vascular beds except for the coronary arteries.¹⁵ Norepinephrine causes greater increase in systemic vascular resistance and diastolic blood pressure, mean arterial pressure, and systolic blood pressure than epinephrine. Venous vasoconstriction decreases venous capacitance, thereby increasing venous return to augment stroke volume and cardiac output. Norepinephrine increases mean arterial pressure primarily by vasoconstriction and to lesser degree by increasing stroke volume and cardiac output. At higher doses, vasoconstriction predominates to an even greater extent. Norepinephrine and epinephrine increase total peripheral vascular resistance more than dobutamine (described in the following text). Unlike epinephrine, norepinephrine has minimal metabolic effects. Hyperglycemia is unlikely to occur as a result of norepinephrine administration. Like epinephrine, norepinephrine dilates coronary arteries.¹⁵ The primary method of elimination is by reuptake into the adrenergic nerve endings where it is stored for subsequent release with only small amounts being metabolized.

Clinical Uses

Norepinephrine is the first-line vasopressor in patients with septic shock.^{5,7} Norepinephrine has more potent α -adrenergic receptor activating properties than epinephrine; it is therefore useful for increasing vascular tone in patients with distributive shock. The primary use of norepinephrine is as a potent vasoconstrictor to increase total peripheral vascular resistance and mean arterial pressure. Norepinephrine is also used for patients with low systemic vascular resistance after cardiopulmonary bypass. In patients with coronary artery disease, norepinephrine can be used to maintain coronary perfusion pressure, although it should be balanced with the resultant increased afterload associated with high doses.

Side Effects

Norepinephrine can exert a favorable effect on right ventricular function,¹⁵ but it should be used cautiously in patients with right ventricular failure. Norepinephrine increases venous return to the heart and also raises pulmonary artery pressures via stimulation of pulmonary vascular α_1 -adrenergic receptors. Both of these may be poorly tolerated by patients with right heart failure.

The use of norepinephrine as an inotropic agent is limited by its action as a potent vasoconstrictor. The increased peripheral resistance and afterload may decrease cardiac output and increase the work of the left ventricle. Its use is also limited by the potential for tachycardia, although its arrhythmogenic potential is less than that of epinephrine and dopamine. One of the major concerns with norepinephrine use is organ ischemia. Excessive vasoconstriction and decreased perfusion of renal, splanchnic, and peripheral vascular beds may lead to end-organ hypoperfusion and ischemia. Renal arteriolar vasoconstriction may lead to oliguria and renal failure. However, when large doses of norepinephrine accompanied by adequate fluid volume resuscitation are used with caution to treat profound hypotension, perfusion pressure and renal blood flow are preserved.¹⁶

Dopamine

Dopamine is an endogenous catecholamine that is the immediate precursor of norepinephrine. Dopamine regulates cardiac, vascular, and endocrine function and is an important neurotransmitter in the central and peripheral nervous systems. The pharmacology of dopamine is complex as this catecholamine differentially stimulates a variety of dopaminergic as well as adrenergic receptors. It is a relatively nonspecific agonist at both dopamine 1 (D_1) and dopamine 2 (D_2) receptors and the α - and β -adrenergic receptors. When activated, D_1 receptors elicit vasodilation in renal, mesenteric, coronary, and cerebral vascular beds and inhibition of sodium-potassium adenosine triphosphatase (Na^+-K^+ ATPase).¹⁶ Activation of these receptors is mediated by adenylate cyclase stimulation. D_2 receptors are principally prejunctional in postganglionic sympathetic

nerves, and when these receptors are activated, norepinephrine release from sympathetic nerve endings is inhibited.^{17,18} D₂ receptors are also present in the pituitary gland, emetic center of the medulla, and kidney. Dopamine receptors may also be associated with the neural mechanism for “reward” that is associated with cocaine and alcohol dependence. Systemic administration of dopamine does not activate these reward centers because dopamine is considered too polar to cross the blood–brain barrier.

Traditionally, the pharmacokinetics of dopamine has been attributed to dose-dependent effects on varying receptors.¹⁷ In reality, there is significant variation between patients and even within the same patient in terms of which receptors are activated at what doses by dopamine.

At low IV infusion rates (0.5-3 µg/kg/minute), dopamine primarily stimulates D₁ and D₂ receptors leading to vasodilation, decreased arterial blood pressure, and increased renal and splanchnic vascular blood flow. Diuresis and natriuresis also occur. The decrease in diastolic blood pressure might lead to a reflex increase in heart rate. At higher infusion rates (3-10 µg/kg/minute), dopamine primarily stimulates β₁-adrenergic receptors in the heart as well as α receptors in the peripheral vasculature. It also induces norepinephrine release from vascular sympathetic neurons. The activation of β receptors leads to increased cardiac output by increasing chronotropy and contractility along with vasodilation and afterload reduction. As the infusion rate is increased even further (>10 µg/kg/minute), dopamine predominantly stimulates α₁ receptors, acting similarly to a pure α agonist. The predominant stimulation of vascular smooth muscle α₁ receptors at these higher doses lead to arterial and venous vasoconstriction, increased systemic vascular resistance, and increased blood pressure attenuating further increases in cardiac output. Reflex bradycardia may also occur at this point.

This aforementioned dose-dependent model of dopamine’s effects is too simplistic, even in healthy individuals. There are a wide range of clinical responses depending on individual variability in pharmacokinetics as well as other variables. For example, despite identical IV infusion rates, there may be a 10- to 75-fold variability in plasma dopamine concentrations produced even in healthy individuals with normal drug metabolism.¹⁹ The etiology of the wide pharmacokinetic variability and variation in individual responses is likely multifactorial, reflecting differences in drug distribution, elimination, and endogenous levels, among other factors. Such differences may be more profound in critically ill patients due to changes in circulating proteins and volume of distribution. Hence, the effects of dopamine cannot be predicted based on the dose,²⁰ and the drug must be titrated to effect.

Rapid metabolism of dopamine with an elimination half-life of 1 to 2 minutes mandates its use as a continuous infusion (1-20 µg/kg/minute) to maintain therapeutic plasma concentrations. Extravasation of dopamine, like norepinephrine, produces intense local vasoconstriction, which may be treated with local infiltration of phentolamine.²¹ Dopamine is not effective orally and does not cross the blood–brain barrier in sufficient amounts to cause CNS effects. The immediate precursor of dopamine, L-dopa, is absorbed from the gastrointestinal tract and readily crosses the blood–brain barrier. Dopamine is partially protein bound. Approximately 25% is converted to norepinephrine. Dopamine undergoes metabolism in the liver with conjugation to sulfates and glucuronides, pulmonary endothelium by catechol-O-methyltransferase (COMT), and excretion by the kidneys.

Clinical Uses

Dopamine is used clinically to increase cardiac output in patients with decreased contractility, low systemic blood pressure, and low urine output as may be present after cardiopulmonary bypass or in chronic heart failure.²⁰ It is unique among the catecholamines in being able to simultaneously increase myocardial contractility, renal blood flow, glomerular filtration rate, excretion of sodium, and urine output.²¹

In patients with cardiogenic shock, dopamine is not preferred over norepinephrine as the first-line agent because a subgroup analysis from a randomized trial found that patients with cardiogenic shock who received dopamine had a much higher mortality rate than those who received norepinephrine.²² In addition, dysrhythmias were more common in the dopamine group.

Renal-Dose Dopamine

The term **renal-dose dopamine** or **low-dose dopamine** refers to the continuous infusion of small doses (1-3 µg/kg/minute) of dopamine to patients to promote renal blood flow. In healthy individuals, low-dose dopamine increases renal blood flow and induces natriuresis and diuresis. Theoretically, dopamine's renal vasodilating effects may be useful in patients with impaired renal function or in patients at risk for decreased renal perfusion as may occur with decreased cardiac output. Dopamine binds to D₁ and D₂ receptors in the proximal tubule, thick ascending loop of Henle, and cortical collecting ducts inhibiting Na⁺-K⁺ ATPase activity, increasing Na⁺ excretion, inducing natriuresis and diuresis.²³ The activation of D₂ in inner medullary collecting ducts stimulates prostaglandin E₂ production. This antagonizes the effects of antidiuretic hormone and results in increased free water clearance. Prostaglandin E₂ enhances blood flow in the inner medulla. Inhibition of aldosterone also increases sodium excretion and diuresis. Hence, dopamine has direct and indirect effects on the renal vasculature in addition to functioning as a diuretic.

The term **renal-dose** or **low-dose dopamine** is misleading as dopamine has many effects at sites other than the kidneys, even at low doses. Dopamine's effects based on dose alone are unpredictable. Low-dose dopamine also implies an unproven beneficial effect on renal function.²⁴⁻²⁶ The use of dopamine after the renal insult has occurred has not been shown to improve glomerular filtration rate. There is evidence that the beneficial effect of low-dose dopamine on renal blood flow and glomerular filtration rate observed in healthy individuals is due to drug-induced increases in cardiac output, and this benefit is lost in early renal failure.²⁶

No randomized controlled studies have demonstrated a decrease in the incidence of acute renal failure when dopamine is administered to patients considered to be at risk for developing acute renal failure in multiple patient populations including major vascular surgery,²⁷ cardiopulmonary bypass, intensive care,²⁸ heart failure, sepsis,²⁹ transplantation, patients exposed to nephrotoxic drugs³⁰ confirming the results of two meta-analyses,^{24,25} finding that dopamine does not prevent or reverse acute renal failure or improve outcome. Low-dose dopamine is associated with multiple complications affecting the cardiovascular, pulmonary, gastrointestinal, endocrine, and immune systems. A multicenter observational study demonstrated that dopamine is an independent risk factor for death for patients with shock due to any cause.³¹ In the absence of data confirming the efficacy of dopamine in preventing acute renal failure, renal-dose dopamine cannot be recommended. In fact, not only does low-dose dopamine not confer to any renal protective mechanism, it may in fact be detrimental.³²

Cardiovascular Effects

Dopamine is associated with dose-dependent sinus tachycardia and the potential to cause ventricular arrhythmias³³ and may predispose to myocardial ischemia by precipitating tachycardia, increasing contractility, increasing afterload, and precipitating coronary artery vasospasm. Dopamine increases peripheral vascular resistance and pulmonary artery pressures.

Gastrointestinal Effects

Gastrointestinal mucosal ischemia and subsequent translocation of bacteria and bacterial toxins play an important role in the development of multiple organ dysfunction syndrome. Dopamine's effect on splanchnic blood flow and gastric intramucosal pH is controversial and inconsistent. There is no evidence that low-dose dopamine has beneficial effects on splanchnic function or reduces the progression to multiorgan failure in sepsis. In septic patients, dopamine but not norepinephrine, as administered to maintain an acceptable mean arterial pressure, resulted in an uncompensated increase in splanchnic oxygen requirements. Although dopamine infusion in septic patients led to increased hepatosplanchic perfusion, hepatosplanchic oxygen uptake was reduced suggesting an impairment of hepatosplanchic metabolism.³⁴ Dopamine agonists interfere with gastrointestinal motility. Low-dose dopamine has been demonstrated to slow gastric motility in mechanically ventilated intensive care patients.³⁵

Endocrine and Immunologic Effects

Dopamine disrupts metabolic and immunologic functions through its effects on hormones and lymphocyte function. In the acute phase of an illness, dopamine induces the pattern of hypopituitarism seen in prolonged

critical illness and chronic stress. When dopamine is used in the chronic phase of illness, it further suppresses the circulating concentrations of pituitary hormones.³⁶ Dopamine depresses the immune status by reducing serum prolactin levels. Prolactin is an immunoregulatory hormone affecting T and B lymphocytes. Dopamine inhibits lymphocyte proliferation, immunoglobulin synthesis, and cytokine production and promotes lymphocyte apoptosis. Dopamine also decreases the secretion of growth hormone, which has anabolic, lipolytic, and immune-stimulating properties. Growth hormone deficiency can contribute to impaired anabolism and a negative nitrogen balance. Dopamine's overall effect is to suppress the secretion and function of anterior pituitary hormones, aggravating catabolism and cellular immune function and inducing central hypothyroidism.³⁶

Respiratory Effects

The infusion of low-dose dopamine in healthy subjects as well as heart failure patients interferes with the ventilatory response to arterial hypoxemia and hypercapnia, reflecting the role of dopamine as an inhibitory neurotransmitter at the carotid bodies.³⁷ The result is depression of ventilation in patients who are being treated with dopamine to increase myocardial contractility.³⁸ Dopamine also decreases arterial oxygen saturation by impairing regional ventilation/perfusion matching in the lungs.³⁹ Dose-dependent reductions in arterial PO_2 with increasing rates of dopamine in critically ill patients after major surgery have been demonstrated.⁴⁰

Intraocular Pressure

Continuous infusions of dopamine to critically ill patients are associated with increases in intraocular pressure.⁴¹ This may create a risk in patients with preexisting glaucoma especially if they are sedated and mechanically ventilated.

Synthetic Catecholamines

The two clinically useful synthetic catecholamines are isoproterenol and dobutamine (see [Table 18.1](#) and [Figure 18.1](#)).

Isoproterenol

Isoproterenol is the most potent activator of all the sympathomimetics with β_1 and β_2 receptor activity. In clinical doses, isoproterenol is devoid of α agonist effects and does not cause the vasoconstriction associated with the naturally occurring catecholamines.

The cardiovascular effects of isoproterenol reflect activation of β_1 receptors in the heart and β_2 receptors in skeletal muscle and to a lesser extent renal and splanchnic vascular beds. In an adult, continuous infusion of isoproterenol, 1 to 5 μg per minute, greatly increases heart rate, myocardial contractility, and cardiac automaticity, whereas vasodilation in skeletal muscles decreases systemic vascular resistance. Although cardiac output may increase thereby increasing systolic blood pressure, the mean arterial pressure may decrease due to decreases in systemic vascular resistance and associated decreases in diastolic blood pressure.

Increases in cardiac output may be attenuated by impaired left ventricular filling due to tachycardia as well as decreased preload from venous vasodilation. Decreased diastolic blood pressure, increased heart rate, and cardiac dysrhythmias may lead to a decrease in coronary blood flow at the same time that myocardial oxygen requirements are increased by tachycardia and increased myocardial contractility.⁴² Compensatory baroreceptor-mediated reflex slowing of the heart rate does not occur during infusion of isoproterenol because mean arterial pressure is not increased. This combination of events may be deleterious in patients with coronary artery disease. Compared to dobutamine, for a comparable increase in cardiac output, isoproterenol is associated with larger decreases in total peripheral vascular resistance and blood pressure.⁴³ It is also associated with more tachycardia both from direct β effects as well as a reflex increase in heart rate with decreased vascular tone. Metabolism of isoproterenol in the liver by COMT is rapid, necessitating a continuous infusion to maintain therapeutic plasma concentrations.

Clinical Uses

A continuous infusion of isoproterenol, 1 to 5 µg per minute, is effective in increasing the heart rate in adults in the presence of heart block. Isoproterenol is used to provide sustained increases in heart rate before insertion of a temporary or permanent cardiac pacemaker in the treatment of bradycardias.

Isoproterenol's ability to decrease pulmonary vascular resistance may be useful in the management of pulmonary hypertension and right ventricular dysfunction.⁴⁴ The use of isoproterenol as an inotropic drug has decreased with the availability of inotropic agents such as dobutamine and phosphodiesterase inhibitors.

Likewise, the use of isoproterenol as a bronchodilator has been supplanted by the availability of specific β_2 agonists.

Adverse Effects

Vasodilation and decreased blood pressure may limit the use of isoproterenol. In addition, it can lead to tachyarrhythmias. The combination of decreased diastolic blood pressure and increased heart rate and dysrhythmias may lead to myocardial ischemia.

Dobutamine

Dobutamine is a synthetic catecholamine derived from isoproterenol consisting of a 50:50 racemic mixture of two stereoisomers.⁴⁵ The (-) enantiomer is a potent α_1 -adrenergic agonist as well as a weak β_1 - and β_2 -adrenergic agonist. The (+) enantiomer is a competitive antagonist at the α_1 receptor site as well as a potent β_1 - and β_2 -adrenergic agonist.⁴⁶ Dobutamine has potent β_1 -adrenergic effects with weaker β_2 -adrenergic activity. Its effect on α receptors increases at higher doses. Dobutamine's cardiovascular effects are a result of the combination of activity of its two stereoisomers.^{46,47}

Dobutamine acts primarily as a positive inotropic agent. Dobutamine leads to an increase in intracellular cAMP, increasing calcium release from the sarcoplasmic reticulum to increase contractility. Cardiac output is increased primarily by an increase in stroke volume. Contractility is increased from its action on myocardial β_1 and α_1 receptors and, to a lesser extent, by decreased afterload from its effect on vascular smooth muscle β_2 receptors. Dobutamine has weak effects on vascular tone causing peripheral vasodilation. At higher doses, the (-) isomer stimulates α_1 receptors, limiting further vasodilation. Blood pressure usually is not significantly affected as α_1 -mediated vasoconstriction by the (-) enantiomer is countered by α_1 antagonism by the (+) enantiomer and by its β_2 activity, although the latter may be unmasked by β blockade therapy.^{46,47}

Dobutamine affects heart rate through its action on β_1 -adrenergic receptors. Dobutamine stimulates sinoatrial node automaticity as well as atrioventricular nodal and ventricular conduction.³³ The increase in calcium that facilitates increased contractility also facilitates increased arrhythmias. At low doses, increases in heart rate may be minimal. However, high doses of dobutamine (>10 µg/kg/minute IV) may predispose the patient to tachycardia and cardiac dysrhythmias. Dobutamine increases myocardial oxygen consumption by increasing tachycardia and myocardial contractility.

Dobutamine causes modest reductions in pulmonary arterial pressure and vascular resistance through its effects on β_2 receptors. In patients with increased pulmonary artery pressure after mitral valve replacement, an infusion of dobutamine (up to 10 µg/kg/minute) increases cardiac output and decreases systemic and pulmonary vascular resistance.⁴⁸ Rapid metabolism of dobutamine (half-life of 2 minutes) necessitates its administration as a continuous infusion of 2 to 10 µg/kg/minute to maintain therapeutic plasma concentrations. Tachyphylaxis may occur as it acts on β -adrenergic receptors. Dobutamine undergoes biotransformation in the liver to inactive glucuronide conjugates and 3-O-methyl dobutamine, most of which is excreted in the urine.⁴⁹

Clinical Uses

Dobutamine produces potent β -adrenergic agonist effects at doses less than 5 µg/kg/minute IV increasing myocardial contractility (β_1 and α_1 receptors) and causing a modest degree of peripheral vasodilation (β_2

receptors). Dobutamine is used to improve cardiac output in patients with heart failure.⁵⁰ Dobutamine is also useful for weaning from cardiopulmonary bypass.⁵¹

It may be of use in patients with pulmonary hypertension, although its effect on the pulmonary vasculature is less than that of the phosphodiesterase inhibitors. Combinations of drugs may be useful to increase the spectrum of activity and improve the distribution of cardiac output. For example, vasodilators may be combined with dobutamine or dopamine to decrease afterload, optimizing cardiac output in the presence of increased systemic vascular resistance. Myocardial oxygen consumption is increased by the increasing tachycardia and contractility, whereas coronary blood flow is decreased by vasodilation.⁴⁹ These properties make dobutamine useful for pharmacologic stress testing to detect potential areas of myocardial ischemia.

The most recent Surviving Sepsis guidelines recommend that a trial of dobutamine infusion be administered or added to preexisting vasopressor therapy in the presence of myocardial dysfunction⁵ defined as elevated cardiac filling pressures and low cardiac output. Therapy with dobutamine is also recommended for patients with ongoing signs of hypoperfusion despite achievement of adequate intravascular volume and mean arterial pressure. These guidelines recommendation, however, are based on a paucity of outcomes data from randomized controlled trials.

Adverse Effects

The use of dobutamine may be limited by the occurrence of tachyarrhythmias, although it is less likely than dopamine or isoproterenol. Sinus tachycardia occurs most commonly, although ventricular arrhythmias may also occur.³³ Tachyarrhythmias occur more frequently at higher dosages or in patients with underlying arrhythmias or heart failure.

Synthetic Noncatecholamines

The commonly used noncatecholamine sympathomimetic drugs are ephedrine and phenylephrine ([Figure 18.5](#)). These will be familiar to every reader.

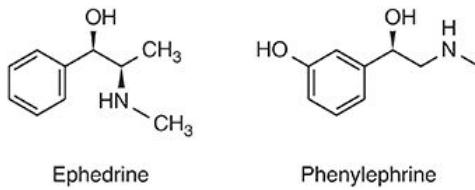


FIGURE 18.5 Synthetic noncatecholamine sympathomimetics.

Ephedrine

Ephedrine is an indirect-acting synthetic sympathomimetic that stimulates α- and β-adrenergic receptors. The pharmacologic effects of ephedrine are partly due to direct stimulation of adrenergic receptors (direct-acting)⁵² and partly due to stimulation of release of endogenous norepinephrine (indirect-acting). Ephedrine is resistant to metabolism by monoamine oxidase in the gastrointestinal tract, thus permitting unchanged drug to be absorbed into the circulation after oral administration. Intramuscular injection of ephedrine is clinically acceptable because drug-induced local vasoconstriction is insufficient to delay systemic absorption or lead to tissue injury.

Ephedrine, unlike epinephrine, does not produce marked hyperglycemia. Mydriasis accompanies the administration of ephedrine, and CNS stimulation does occur, although less than that produced by amphetamine.

Clinical Uses

Ephedrine, 5 to 10 mg IV administered to adults, is a commonly selected sympathomimetic to increase systemic blood pressure in the presence of sympathetic nervous system blockade produced by regional anesthesia or hypotension due to inhaled or injected anesthetics. In an animal model, ephedrine more

specifically corrected the noncardiac circulatory changes produced by spinal anesthesia than did a selective α or β agonist drug.⁵³ For many years, ephedrine was considered the preferred sympathomimetic for administration to parturients experiencing decreased systemic blood pressure owing to spinal or epidural anesthesia. Support for this practice was the observation in pregnant ewes that uterine blood flow was not greatly altered when ephedrine was administered to restore maternal blood pressure to normal after sympathetic nervous system blockade.⁵⁴ Recent reviews of trials of ephedrine versus phenylephrine have concluded that systemic blood pressure control is similar with both drugs but phenylephrine is associated with a higher umbilical artery pH at delivery than ephedrine.⁵⁴ Administration of phenylephrine by infusion during cesarean section to maintain maternal systolic blood pressure at baseline is associated with a lower incidence of fetal acidosis than is ephedrine.⁵⁵ Based on these data, it seems that α agonists such as phenylephrine may be preferable to ephedrine for treatment of maternal hypotension.

Ephedrine, 0.5 mg/kg intramuscularly, has an antiemetic effect similar to that of droperidol but with less sedation when administered to patients undergoing outpatient laparoscopy using general anesthesia.⁵⁶

Cardiovascular Effects

The cardiovascular effects of ephedrine resemble those of epinephrine, but its systemic blood pressure-elevating response is less intense and lasts longer. The IV ephedrine results in increases in systolic and diastolic blood pressure, heart rate, and cardiac output. Renal and splanchnic blood flows are decreased, whereas coronary and skeletal muscle blood flows are increased. Systemic vascular resistance may be altered minimally because vasoconstriction in some vascular beds is offset by vasodilation (β_2 stimulation) in other areas. These cardiovascular effects are due, in part, to α receptor-mediated peripheral arterial and venous vasoconstriction. The principal mechanism, however, for cardiovascular effects produced by ephedrine is increased myocardial contractility due to activation of β_1 receptors. In the presence of preexisting β -adrenergic blockade, the cardiovascular effects of ephedrine may resemble responses more typical of α -adrenergic receptor stimulation.

Phenylephrine

Phenylephrine, 3-hydroxyphenylethylamine, is a synthetic noncatecholamine. Phenylephrine differs from epinephrine only in lacking a 4-hydroxyl group on the benzene ring. Clinically, phenylephrine mimics the effects of norepinephrine but is less potent and longer lasting. Phenylephrine principally stimulates α_1 -adrenergic receptors by a direct effect, with only a small part of the pharmacologic response being due to its ability to evoke the release of norepinephrine (indirect-acting).⁵⁷ Phenylephrine exerts minimal effects on β -adrenergic receptors. The dose of phenylephrine necessary to stimulate α_1 receptors is far less than the dose that stimulates α_2 receptors. Phenylephrine primarily causes venoconstriction rather than arterial constriction. The CNS stimulation is minimal.

Clinical Uses

Phenylephrine, 50 to 200 μ g IV bolus, is often administered to adults to treat systemic blood pressure decreases that accompany sympathetic nervous system blockade produced by a regional anesthetic and peripheral vasodilation following administration of IV or inhaled anesthetics.⁵⁸ Phenylephrine is believed to be particularly useful in patients with coronary artery disease and in patients with aortic stenosis because it increases coronary perfusion pressure without chronotropic side effects, unlike most other sympathomimetics. Phenylephrine has been used as a continuous infusion (20-100 μ g per minute) in adults to maintain normal blood pressure during surgery. The reflex vagal effects produced by phenylephrine can be used to slow heart rate in the presence of hemodynamically significant supraventricular tachydysrhythmias.

Due to the potential for decreasing stroke volume, the Surviving Sepsis guidelines do not recommend phenylephrine for the treatment of septic shock unless patients experience serious arrhythmias with norepinephrine, have high cardiac output, or require salvage therapy.⁵

Cardiovascular Effects

Rapid IV injection of phenylephrine to patients with coronary artery disease produces dose-dependent peripheral vasoconstriction and increases in systemic blood pressure, which are accompanied by decreases in cardiac output (**Figure 18.6**).⁵⁹ Decreases in cardiac output may reflect increased afterload but more likely are due to baroreceptor-mediated reflex bradycardia in response to drug-induced increases in diastolic blood pressure. It is possible that decreases in cardiac output could limit the associated increases in systemic blood pressure. Rapid administration of phenylephrine, 1 µg/kg IV, to anesthetized patients with coronary artery disease causes a transient impairment of left ventricular global function.⁶⁰ Oral clonidine premedication augments the pressor response to phenylephrine, presumably due to clonidine-induced potentiation of α_1 -mediated vasoconstriction.⁶¹ Renal, splanchnic, and cutaneous blood flows are decreased, but coronary blood flow is increased. Pulmonary artery pressure is increased by phenylephrine.

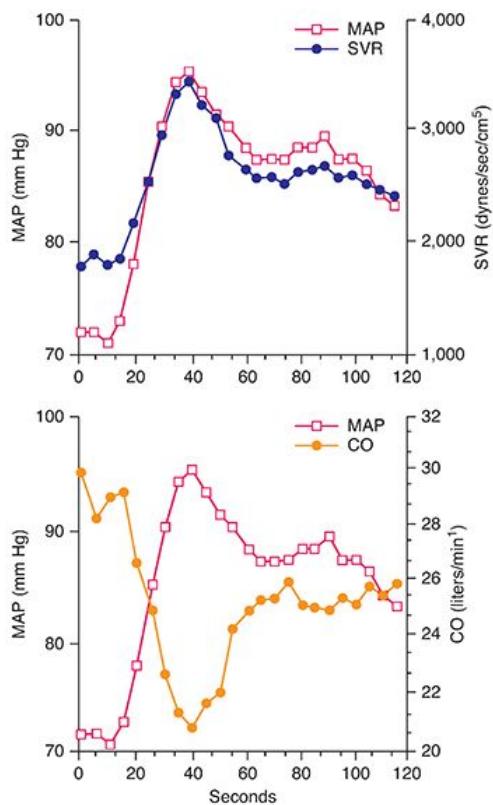


FIGURE 18.6 Hemodynamic response to rapid intravenous injection of phenylephrine in a single patient. Mean arterial pressure (MAP) and systemic vascular resistance (SVR) increase, and cardiac output (CO) decreases in response to phenylephrine, with peak effects occurring 42 seconds after drug administration. Reprinted with permission from Schwinn DA, Reeves JG. Time course and hemodynamic effects of alpha-1-adrenergic bolus administration in anesthetized patients with myocardial disease. Anesth Analg. 1989;68(5):571-578. Copyright © 1989 International Anesthesia Research Society.

Treatment of Overdose

Systemic manifestations of sympathetic nervous system activation (systemic hypertension, tachycardia, baroreceptor-mediated bradycardia) may accompany vascular absorption of α agonists (phenylephrine, epinephrine) when used as topical or injected vasoconstrictors in the surgical field. Phentolamine, an α_1 -adrenergic receptor antagonist, is an appropriate pharmacologic choice for phenylephrine toxicity.⁶² Because β_1 receptor blockade reduces cardiac output, treatment of phenylephrine-induced hypertensive crisis with β -adrenergic blocking drugs is *contraindicated*. However, systemic hypertension induced by intravenously administered α agonists may not require treatment. The duration of action of IV phenylephrine and

epinephrine is brief and hypertension may resolve spontaneously without pharmacologic interventions. Severe hypertension may require pharmacologic interventions, but treatment must not decrease the ability of the stressed myocardium to increase contractility and heart rate. In this circumstance, vasodilating drugs such as nitroprusside or nitroglycerin may be helpful.

Selective β_2 -Adrenergic Agonists

Selective β_2 -adrenergic agonists relax bronchiole and uterine smooth muscle but in contrast to isoproterenol generally lack stimulating (β_1) effects on the heart. Nevertheless, high concentrations of these drugs are likely to cause stimulation of β_1 receptors. The chemical structure of selective β_2 -adrenergic agonists (placement of hydroxyl groups on the benzene ring at sites different than the catecholamines) renders them resistant to methylation by COMT, thus contributing to their sustained duration of action. The commonly used β_2 -adrenergic agonists are albuterol, metaproterenol, and terbutaline (Figure 18.7) (Table 18.2).

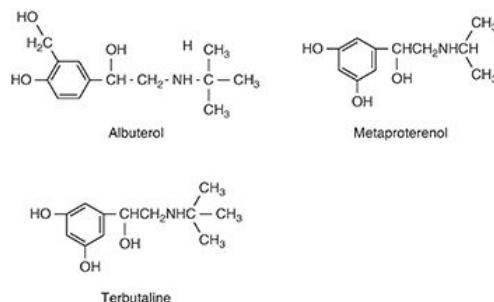


FIGURE 18.7 Selective β_2 -adrenergic agonists.

TABLE 18.2

Comparative pharmacology of selective β_2 -adrenergic agonist bronchodilators

	β_2 Selectivity	Peak effect (minutes)	Duration of action (hour)	Concentration (μ g per puff)	Method of administration
Albuterol	High	30-60	4	90	MDI, oral
Metaproterenol	Moderate	30-60	3-4	200	Oral, subcutaneous
Terbutaline	High	60	4	200	MDI, oral, subcutaneous

Abbreviation: MDI, metered-dose inhaler.

Clinical Uses

β_2 -Adrenergic agonists are the preferred treatment for acute episodes of asthma and the prevention of exercise-induced asthma.⁶³ Currently used β_2 -adrenergic agonists may be divided into those with an intermediate duration of action (3-6 hours) and those that are long acting (>12 hours).⁶³ Among the intermediate-acting drugs, there is little reason to choose one over the other. β_2 -Adrenergic agonists are also used regularly in patients with chronic obstructive pulmonary disease, resulting in improved air flow and exercise tolerance. The long-acting β_2 -adrenergic agonist salmeterol is highly lipophilic and has a high affinity for the β_2 receptor, resulting in prolonged activation at this site. In addition to the treatment of bronchospasm, β_2 -adrenergic agonists may also be administered as continuous infusions to stop premature uterine contractions (tocolytics).

Route of Administration

β_2 -Adrenergic bronchodilators can be administered orally, by inhalation, subcutaneously, or intravenously. The inhaled route is preferred because the side effects are fewer for any given degree of bronchodilation. Inhalation is as effective as parenteral administration for treating acute, severe attacks of asthma in most patients, although some who have severe bronchial obstruction may benefit initially from parenteral therapy.

Inhaled β_2 -adrenergic agonists can be administered as an aerosol from a jet or ultrasonic nebulizer or they can be administered from a metered-dose inhaler either as a propellant-generated aerosol or as a breath-propelled dry powder. With optimal inhalation technique (discharge the inhaler while taking a slow deep breath over 5-6 seconds and then hold the breath at full inspiration for 10 seconds), approximately 12% of the drug is delivered from the metered-dose inhaler to the lungs; the remainder is deposited in the mouth, pharynx, and larynx.⁶³ The presence of an endotracheal tube decreases by approximately 50% to 70% the amount of drug delivered by a metered-dose inhaler that reaches the trachea.⁶⁴ Actuation of the metered-dose inhaler during a mechanically delivered inspiration increases the amount of drug that passes beyond the distal end of the tracheal tube.

Side Effects

The widespread distribution of β_2 -adrenergic receptors makes it likely that undesired responses may result when β_2 -adrenergic agonists undergo systemic absorption. The ability to minimize these systemic side effects by decreasing plasma drug concentrations is an advantage of administering β_2 -adrenergic bronchodilators by inhalation.

The principal side effect in awake subjects of β_2 -adrenergic agonists treatment is tremor, which is caused by direct stimulation of β_2 receptors in skeletal muscles. Increased heart rate is less common with the selective β_2 -adrenergic agonists, but even stimulation of β_2 receptors may result in vasodilation and reflex tachycardia. As there are β_2 -adrenergic receptors in the heart, direct stimulation of the heart results from the use of selective β_2 -adrenergic agonists. In patients with acute, severe asthma, β_2 -adrenergic agonists may cause a transient decrease in arterial oxygenation presumed to reflect relaxation of compensatory vasoconstriction in areas of decreased ventilation.

Lactic acidosis may occur in association with β_2 agonist therapy, perhaps reflecting excess glycogenolysis and lipolysis from β_2 receptor activation.⁶⁵

Albuterol

Albuterol is the preferred selective β_2 -adrenergic agonist for the treatment of acute bronchospasm due to asthma. Administration is most often by metered-dose inhaler, producing about 100 μg per puff; the usual dose is two puffs delivered during deep inhalations 1 to 5 minutes apart. This dose may be repeated every 4 to 6 hours, not to exceed 16 to 20 puffs daily. Alternatively, 2.5 to 5 mg of albuterol (0.5-1 mL of 0.5% solution in 5 mL of normal saline) may be administered by nebulization every 15 minutes for three to four doses, followed by treatments hourly during the initial hours of therapy. The duration of action of an inhaled dose is about 4 hours, but significant relief of symptoms may persist up to 8 hours. The effects of albuterol and volatile anesthetics on bronchomotor tone are additive.⁶⁶

Continuous nebulization of albuterol using a large reservoir system to deliver up to 15 mg per hour for 2 hours may be appropriate and necessary in the presence of life-threatening asthma. Tachycardia and hypokalemia may accompany these large doses of albuterol. Nevertheless, larger doses and more frequent dosing intervals for inhaled β -adrenergic agonist therapy are needed in acute severe asthma due to decreased deposition at the site of action (low tidal volumes and narrowed airways), alteration in the dose-response curve, and altered duration of activity. Inhaled albuterol (four puffs) blunts airway responses to tracheal intubation in asthmatic patients.⁶⁷

Metaproterenol

Metaproterenol is a selective β_2 -adrenergic agonist used to treat asthma. Administered by metered-dose inhaler, the daily dosage should not exceed 16 puffs, with each metered-aerosol actuation delivering approximately 650 μg .

Terbutaline

Terbutaline is a predominantly β_2 -adrenergic agonist that may be administered orally, subcutaneously, or by inhalation to treat asthma. Terbutaline is used frequently by oral route to suppress labor. The subcutaneous administration of terbutaline (0.25 mg) produces responses that resemble those of epinephrine, but the duration of action is longer. The subcutaneous dose of terbutaline for children is 0.01 mg/kg. Administered by metered-dose inhaler, the daily dose should not exceed 16 to 20 puffs, with each metered-dose actuation delivering about 200 μg .

Cardiac Glycosides

Digitalis is the term used for cardiac glycosides that occur naturally in many plants, including the foxglove plant. Digoxin, digitoxin, and ouabain are examples of clinically useful cardiac glycosides ([Figure 18.8](#)). Of these, only digoxin remains commonly used.

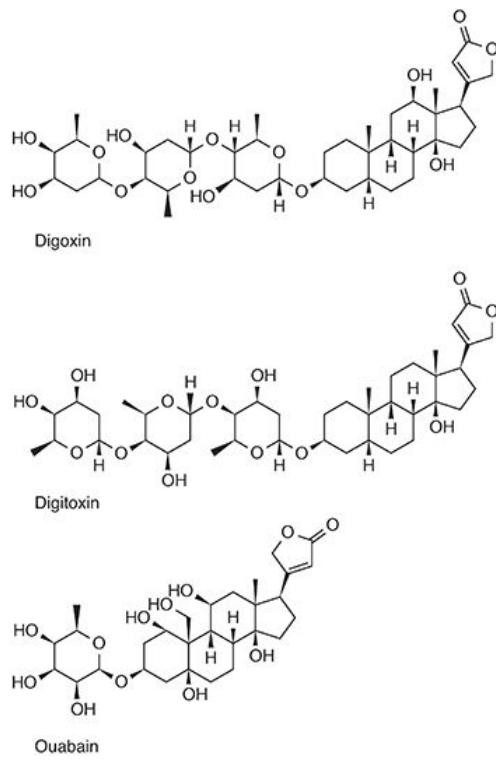


FIGURE 18.8 Cardiac glycosides.

Digoxin

Digoxin is used most often during the perioperative period for the management of supraventricular tachydysrhythmias (paroxysmal atrial tachycardia, atrial fibrillation, atrial flutter) associated with a rapid ventricular response rate based on the ability of these drugs to slow conduction of cardiac impulses through the atrioventricular node. The use of digoxin to treat acute decreases in left ventricular contractility is uncommon because of the availability of more efficacious drugs. Heart failure patients treated with digoxin have a lower incidence of hospitalizations but their mortality is not decreased.[68,69](#) Based on this observation, digoxin may be selected only for treatment of symptoms that persist after a comprehensive neurohormonal blockade (angiotensin-converting enzyme inhibitors, β -adrenergic antagonists, aldosterone antagonists),

which have been shown to decrease overall mortality in heart failure patients.⁶⁸ Nevertheless, digoxin continues to have an important therapeutic role in the treatment of chronic heart failure.

Direct current cardioversion in the presence of digoxin toxicity may be hazardous because of increased risk of developing cardiac dysrhythmias, including ventricular fibrillation. Hypokalemia should be corrected and lidocaine IV should be prophylactically given to decrease the likelihood of a ventricular dysrhythmias. Digoxin may be harmful in patients with hypertrophic subaortic stenosis because increased myocardial contractility intensifies the resistance to ventricular ejection.

Pharmacokinetics

The bioavailability of oral digoxin is 60% to 80%.⁷⁰ In some patients, the digoxin levels may be reduced by up to 40% due to digestion by colonic bacteria. Peak plasma concentrations are observed 1 to 3 hours following oral administration. Following IV administration, the bioavailability is 100%, and peak plasma concentrations are observed immediately following administration as expected for all drugs. Digoxin is eliminated almost entirely by renal excretion, with a half-life of 1 to 2 days. The half-life is inversely proportional to glomerular filtration rate and thus increases with age or renal disease.

Figure 18.9 shows the plasma and effect site time course of 0.5 mg of digoxin, given either orally (**Figure 18.9A**) or intravenously (**Figure 18.9B**), based on the pharmacokinetic model of Jelliffe et al.⁷¹ The time course of digoxin is reflected in the effect site concentration, shown in red, rather than the plasma concentration, shown in blue. The effect site is thought to include the myocardium, along with most other tissues.

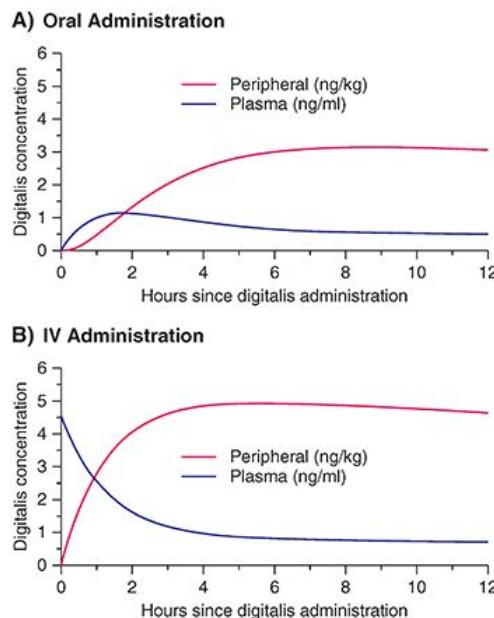


FIGURE 18.9 Simulated plasma (blue line) and peripheral (red line) concentrations of digoxin following a 0.5-mg oral (A) or intravenous (B) dose. *The simulation is based on the pharmacokinetic model of Jelliffe RW, Milman M, Schumitzky A, et al. A two-compartment population pharmacokinetic-pharmacodynamic model of digoxin in adults, with implications for dosage. Ther Drug Monit. 2014;36(3):387-393.*

The onset time for oral digoxin is 0.5 to 2 hours, with a peak effect about 6 hours after ingestion. With IV use, the onset time is 10 to 30 minutes, with a peak effect 2 to 4 hours after administration. After achievement of therapeutic plasma concentrations of digoxin by either the oral or IV route, the maintenance oral dose is adjusted according to the individual patient's response, the electrocardiogram (ECG), and the plasma concentration of digoxin.

Mechanism of Action

The complex mechanisms of the positive inotropic effect evoked by cardiac glycosides include direct effects on the heart that modify its electrical and mechanical activity and indirect effects evoked by reflex alterations in autonomic nervous system activity. Cardiac glycosides selectively and reversibly inhibit the $\text{Na}^+ \text{-K}^+$ ATPase ion transport system (sodium pump) located in the sarcolemma (cell wall) of cardiac cells. Cardiac glycosides bind to the α subunit on the extracellular surface of the ATPase enzyme, inducing a conformational change that interferes with outward transport of sodium ions across cardiac cell membranes. The result is an increase in intercellular sodium. A second transporter is the sodium-calcium exchanger, which transports calcium out of the cell in exchange for sodium. Intracellular sodium accumulates when the sodium-potassium exchanger is blocked by cardiac glycosides. The resulting increase in cellular sodium ion concentration in turn blocks the sodium-calcium exchanger and increases intracellular calcium. Increased intracellular calcium is the primary mechanism of inotropic action for digitalis and related cardiac glycosides. The positive inotropic effects produced by cardiac glycosides occur without changes in heart rate and are associated with decreases in left ventricular preload, afterload, wall tension, and oxygen consumption in the failing heart.⁷²

The principal cardiovascular effect of digitalis glycosides administered to patients with cardiac failure is a dose-dependent increase in myocardial contractility that becomes significant with less than full digitalizing doses. The positive inotropic effect manifests as increased stroke volume, decreased heart size, and decreased left ventricular end-diastolic pressure (LVEDP). Indeed, cardiac glycosides can double stroke volume from a failing and dilated left ventricle. The ventricular function curve (Frank-Starling curve) is shifted to the left ([Figure 18.10](#)). Improved renal perfusion due to an overall increase in cardiac output favors mobilization and excretion of edema fluid, accounting for the diuresis that often accompanies the administration of cardiac glycosides to patients in cardiac failure. Excessive sympathetic nervous system activity that occurs as a compensatory response to cardiac failure is decreased with the improved circulation that accompanies administration of cardiac glycosides. The resulting decrease in systemic vascular resistance further enhances forward left ventricular stroke volume.

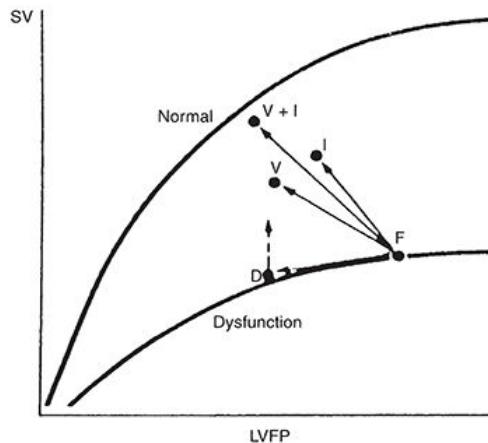


FIGURE 18.10 Cardiac glycosides shift the ventricular function curve of the failing myocardium to the left. Abbreviations: LVFP, left ventricular filling pressure; SV, stroke volume.

Cardiac glycosides also increase myocardial contractility in the absence of cardiac failure. Nevertheless, the resulting tendency for cardiac output to increase may be offset by decreases in heart rate and direct vasoconstricting effects of cardiac glycosides on arterial and, to a lesser extent, venous smooth muscle. Indeed, cardiac output is often unchanged or even decreased when cardiac glycosides are administered to patients with normal hearts.

In addition to positive inotropic effects, cardiac glycosides enhance parasympathetic nervous system activity, leading to delayed conduction of cardiac impulses through the atrioventricular node and decreases in heart rate. The magnitude of this negative dromotropic and chronotropic effect depends on the preexisting activity of the autonomic nervous system. Increased parasympathetic nervous system activity decreases

contractility in the atria, but direct positive inotropic effects of cardiac glycosides more than offset these nervous system–induced negative inotropic effects on the ventricles.

The electrophysiologic effects of therapeutic plasma concentrations of cardiac glycosides manifest on the ECG as (1) prolonged P-R intervals due to delayed conduction of cardiac impulses through the atrioventricular node, (2) shortened QTc intervals because of more rapid ventricular repolarization, (3) ST segment depression (scaphoid or scooped out) due to a decreased slope of phase 3 depolarization of cardiac action potentials, and (4) diminished amplitude or inversion of T waves. The P-R interval is rarely prolonged to longer than 0.25 second, and the effect on the QTc interval is independent of parasympathetic nervous system activity. Changes in the ST segment and T wave do not correlate with therapeutic plasma concentrations of cardiac glycosides. Furthermore, ST-segment and T-wave changes on the ECG may suggest myocardial ischemia. When digitalis is discontinued, the changes on the ECG disappear in several weeks.

Toxicity

Cardiac glycosides have a narrow therapeutic range. The serum digoxin concentration does not necessarily correlate with toxicity. Numerous reports have described asymptomatic patients with a “toxic” level, whereas others describe patients with significant toxicity symptoms but with a serum digoxin level in the therapeutic range.⁷³ The most frequent cause of digitalis toxicity in the absence of renal dysfunction is the concurrent administration of diuretics that cause potassium depletion. Hypokalemia probably increases myocardial binding of cardiac glycosides, resulting in an excess drug effect. Indeed, binding of cardiac glycosides to the Na⁺-K⁺ ATPase enzyme complex is inhibited by increases in the plasma concentration of potassium. Other electrolyte abnormalities that contribute to digitalis toxicity include hypercalcemia and hypomagnesemia. An increase in sympathetic nervous system activity as produced by arterial hypoxemia increases the likelihood of digitalis toxicity.

Elderly patients with decreased renal function are vulnerable to the development of digitalis toxicity if usual doses of digoxin are administered. Impaired renal function and electrolyte changes (hypokalemia, hypomagnesemia) that may accompany cardiopulmonary bypass could predispose the patient to the development of digitalis toxicity.

Diagnosis

Determination of the plasma digoxin concentration may be useful to indicate the likely presence of digitalis toxicity. A plasma digoxin concentration of less than 0.5 ng/mL eliminates the possibility of digitalis toxicity. Plasma concentrations between 0.5 and 2.5 ng/mL are usually considered therapeutic, but some patients can have toxicity even at this range. Levels greater than 3 ng/mL are in a toxic range. Infants and children have an increased tolerance to cardiac glycosides, and their range of therapeutic concentrations for digoxin is 2.5 to 3.5 ng/mL. Anorexia, nausea, and vomiting are early manifestations of digitalis toxicity. These symptoms, when present preoperatively in patients receiving cardiac glycosides, should arouse suspicion of digitalis toxicity.

There are no unequivocal features on the ECG that confirm the presence of digitalis toxicity.⁷⁴ Nevertheless, toxic plasma concentrations of digitalis typically cause atrial or ventricular cardiac dysrhythmias (increased automaticity) and delayed conduction of cardiac impulses through the atrioventricular node (prolonged P-R interval on the ECG), culminating in incomplete to complete heart block. Atrial tachycardia with block is the most common cardiac dysrhythmia attributed to digitalis toxicity. Activity of the sinoatrial node may also be directly inhibited by high doses of cardiac glycosides. Conduction of cardiac impulses through specialized conducting tissues of the ventricles is not altered, as evidenced by the failure of even toxic plasma concentrations of digoxin to alter the duration of the QRS complex on the ECG. Ventricular fibrillation is the most frequent cause of death from digitalis toxicity.

Treatment

Treatment of digitalis toxicity includes (1) correction of predisposing causes (hypokalemia, hypomagnesemia, arterial hypoxemia), (2) administration of drugs (phenytoin, lidocaine, atropine) to treat cardiac dysrhythmias, and (3) insertion of a temporary artificial transvenous cardiac pacemaker if complete

heart block is present. Supplemental potassium decreases the binding of digitalis to cardiac muscle and directly antagonizes the cardiotoxic effects of cardiac glycosides. Serum potassium concentrations should be determined before treatment because supplemental potassium in the presence of a high preexisting plasma level of potassium will intensify atrioventricular block and depress the automaticity of ectopic pacemakers in the ventricles, leading to complete heart block. Phenytoin (0.5-1.5 mg/kg IV over 5 minutes) or lidocaine (1-2 mg/kg IV) are effective in suppressing ventricular cardiac dysrhythmias caused by digitalis. Phenytoin is also effective in suppressing atrial dysrhythmias. Atropine, 35 to 70 µg/kg IV, can be administered to increase heart rate by offsetting excessive parasympathetic nervous system activity produced by toxic plasma concentrations of digitalis. Propranolol is effective in suppressing increased automaticity produced by digitalis toxicity, but its tendency to increase atrioventricular node refractoriness limits its usefulness when conduction blockade is present. Life-threatening digitalis toxicity can be treated by administering digoxin antibodies,⁷⁵ decreasing the plasma concentration of digoxin. The digoxin-antibody complex is eliminated by the kidneys. Hemodialysis is not recommended for digoxin removal due to high tissue distribution of the drug at steady state.

Drug Interactions

Sympathomimetics with β-adrenergic agonist effects may increase the likelihood of cardiac dysrhythmias in the presence of cardiac glycosides.⁷⁶ The IV administration of calcium may precipitate cardiac dysrhythmias in patients receiving cardiac glycosides. Any drug that facilitates renal loss of potassium increases the likelihood of hypokalemia and associated digitalis toxicity. The simultaneous administration of an oral antacid and digitalis decreases the gastrointestinal absorption of cardiac glycosides. Fentanyl, enflurane, and, to a lesser extent, isoflurane protect against digitalis-enhanced cardiac automaticity.⁷⁷

Selective Phosphodiesterase Inhibitors

Phosphodiesterase inhibitors are a heterogeneous group of noncatecholamine nonglycoside compounds that exert a competitive inhibitory action on phosphodiesterase enzymes. Multiple types of phosphodiesterase enzymes exist in different tissues (cardiac muscle, vascular smooth muscle, platelets, liver, and lungs) possessing different cyclic nucleotide substrate specificity. Selective phosphodiesterase inhibitors exert different physiologic effects depending on their enzyme fraction specificity.⁷⁸ Selective inhibitors of phosphodiesterase fraction III (PDE III) (**Figure 18.11**) decrease the hydrolysis of cAMP, leading to increased intracellular concentrations of cAMP in the myocardium and vascular smooth muscle. They also have an indirect effect on cyclic guanosine monophosphate-dependent protein kinase in vascular smooth muscle. In myocardium, increased intracellular cAMP concentrations result in stimulation of protein kinases that phosphorylate the sarcoplasmic reticulum, increasing inward calcium current, increasing intracellular calcium and contractility. In vascular smooth muscle, increased cAMP decreases calcium available for contraction by facilitating the uptake of calcium by the sarcoplasmic reticulum, leading to smooth muscle relaxation and vasodilation. Although PDE III isoenzymes exist in airway smooth muscle, bronchodilation is not a predominant clinical effect of the current cardiac-selective PDE III inhibitors.

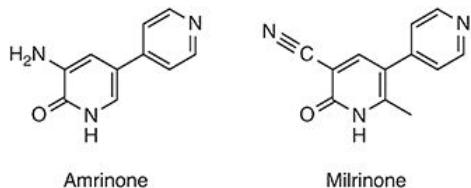


FIGURE 18.11 Selective inhibitors of phosphodiesterase subtype III, amrinone and milrinone.

The overall effect of selective PDE III inhibitors is to combine positive inotropic effects with smooth muscle relaxation in both arteriolar and venous beds. Hence, they have been termed **inodilators**. Physiologic effects include increased contractility, increased cardiac output, and decreased LVEDP in addition to increased venous capacitance, decreased filling pressures (central venous pressure and pulmonary capillary wedge pressure), and decreased venous return to the heart. Mean pulmonary artery pressures and pulmonary

and systemic vascular resistance are decreased. Selective PDE III inhibitors also improve the lusitropic (relaxed) state of the heart.⁷⁹ Diastolic relaxation is facilitated by enhanced calcium removal from the sarcoplasm, thereby improving ventricular filling.

These inodilators decrease preload and afterload. Hence, theoretically, wall tension and myocardial oxygen consumption should decrease, in contrast to dobutamine, which increases myocardial oxygen consumption as it increases contractility.

Selective PDE III inhibitors act independently of β -adrenergic receptors and will increase myocardial contractility in patients with myocardial depression from β receptor blockade and in patients who have downregulation of β -adrenergic receptors and are refractory to catecholamine therapy. The effects of catecholamines, which also increase cAMP concentrations but through β -adrenergic stimulation, are potentially enhanced by PDE III inhibition. The hemodynamic response to selective PDE inhibitors exceeds that of cardiac glycosides and is synergistic to the actions of catecholamines. These drugs can be used in conjunction with digitalis without provoking digitalis toxicity. The PDE III inhibitors have their greatest clinical usefulness in patients who would benefit from combined inotropic and vasodilator therapy.

Milrinone

Milrinone is a bipyridine derivative of amrinone with almost 30 times the inotropic potency of amrinone but less adverse side effects. Because of its reduced incidence of side effects, milrinone has replaced amrinone in clinical use. Cardiac output improves both as a result of increased inotropy as well as vascular smooth muscle relaxation of peripheral and pulmonary vessels.⁸⁰ Dose-dependent increases in cardiac index occur with minimal increases in myocardial oxygen consumption. Decreases in LVEDP, mean arterial pressure, central venous pressure, pulmonary artery occlusion pressure, pulmonary vascular resistance, and systemic vascular resistance occur as well as improvements in diastolic function.⁸¹

Milrinone is administered as an IV bolus of 50 $\mu\text{g}/\text{kg}$ over 10 minutes followed by a continuous infusion of 0.375 to 0.75 $\mu\text{g}/\text{kg}/\text{minute}$ to maintain plasma milrinone concentrations at or above therapeutic levels.⁸² A bolus dose of 50 $\mu\text{g}/\text{kg}$ was found to be as effective as a dose of 75 $\mu\text{g}/\text{kg}$ with fewer side effects and more effective than a dose of 25 $\mu\text{g}/\text{kg}$.⁸³ The maximum daily dose of milrinone should not exceed 1.3 mg/kg/day. Approximately 70% of the drug in circulation is protein bound. The elimination half-time is 2.7 hours, and about 80% of the drug is excreted unchanged by the kidneys with a minor part undergoing glucuronide conjugation before excretion. The dose should be decreased in patients with severe renal dysfunction.

Clinical Uses

Milrinone may be useful in the management of acute left ventricular dysfunction such as after cardiac surgery. Successful weaning of high-risk patients from cardiopulmonary bypass may be enhanced by administration of milrinone.⁸³⁻⁸⁵ Milrinone may potentiate the effects of adrenergic agents as well as help increase inotropy in chronic heart failure patients who have downregulation of β_1 -adrenergic receptors. In patients with congestive heart failure, symptomatic and hemodynamic improvements as well as improvement in exercise have been reported, although milrinone use does not slow the natural progression of disease.⁸⁶ Routine short-term milrinone treatment for acute exacerbation of chronic heart failure without hypotension from a low cardiac output state is not supported,⁸⁷ although milrinone may be used as a bridge to orthotopic heart transplantation. It is particularly useful in the setting of pulmonary hypertension. Milrinone decreases pulmonary artery pressures more effectively than other positive inotropic agents, even dobutamine.^{88,89} The inotropic effects of milrinone are reduced by acidosis, presumably reflecting decreased cAMP formation in acidotic muscle.⁹⁰

Both milrinone and dobutamine improve cardiac index and decrease cardiac filling pressures, although milrinone may be more effective for the latter with significant reductions in right and left heart filling pressures. Milrinone is associated with more vasodilation and greater decreases in systemic vascular resistance and blood pressure than dobutamine. Unlike dobutamine, milrinone rarely causes tachycardia. Both agents may increase myocardial oxygen consumption with milrinone doing so to a lesser extent. The choice between dobutamine and milrinone may be based on hemodynamic differences. Milrinone may be preferred

in situations with high filling pressures, elevated pulmonary artery pressure, need for continued β blockade, decreased responsiveness to catecholamine therapy, and increased risk for tachyarrhythmias. Dobutamine may be preferred in situations with significant vasodilation or renal dysfunction.

Milrinone has the additional role of being able to reverse vasospasm in arterial grafts.⁹¹ Milrinone is also thought to have antiinflammatory effects, and thus, perioperative administration may dilate splanchnic vasculature and attenuate systemic inflammation in the acute phase response after cardiopulmonary bypass.⁹²

Side Effects

Rapid administration of milrinone may decrease systemic vascular resistance, decrease venous return, and result in hypotension. The hypotension may be attenuated by slower bolus administration and concomitant administration with vasopressors. Despite its beneficial hemodynamic actions, chronic oral therapy with milrinone may increase morbidity and mortality in patients with severe chronic heart failure and is not approved by the U.S. Food and Drug Administration for this indication.⁹³ The mechanism for this remains unknown, although a proarrhythmic effect has been suggested. Because of its higher potency, milrinone has less of an effect on platelets than amrinone. Although both agents inhibit in vitro platelet aggregation, short-term milrinone use did not cause significant changes in platelet number or function after cardiopulmonary bypass beyond the usual effects of cardiopulmonary bypass and cardiac surgery.⁹⁴

Calcium

Calcium is present in the body in greater amounts than any other mineral. Calcium is important for (1) neuromuscular transmission, (2) skeletal muscle contraction, (3) cardiac muscle contractility, (4) blood coagulation, and (5) exocytosis necessary for release of neurotransmitters. In addition, calcium is the principal component of bone. The cytoplasmic concentration of ionized calcium is maintained at low levels by extrusion from the cells and sequestration of calcium ions within cellular organelles, particularly mitochondria, and in the sarcoplasmic reticulum of skeletal muscles. The large gradient for calcium across cell membranes, or across the membranes of calcium storing organelles, is essential for calcium's role in transmembrane signaling in response to various electrical or chemical stimuli.

Calcium is a potent inotrope. Increasing the plasma concentrations of ionized calcium with exogenous administration of calcium chloride or calcium gluconate is commonly used to treat cardiac depression as may accompany delivery of volatile anesthetics, transfusion of citrated blood, and following termination of cardiopulmonary bypass. Calcium is necessary for excitation-contraction coupling in vascular smooth muscle and may result in a vasoconstricting effect on coronary arteries that impairs coupling of coronary blood flow to augment myocardial oxygen demand.⁹⁵

Calcium Measurement

The plasma concentration of calcium is maintained between 4.3 and 5.3 mEq/L (8.5-10.5 mg/dL) by endocrine control of ion transport in the kidney, intestine, and bone, mediated by vitamin D, parathyroid hormone, and calcitonin.⁹⁶ Total plasma calcium consists of (1) calcium bound to albumin, (2) calcium complexed with citrate and phosphorus ions, and (3) freely diffusible ionized calcium. As would be expected, total plasma calcium decreases with low serum albumin and with hypophosphatemia.

It is the ionized calcium, and not the total plasma calcium, that produces the physiologic effects of calcium. Therefore, hypoalbuminemia and hypophosphatemia typically are not associated with signs of hypocalcemia. Conversely, large transfusions may be associated with acute hypocalcemia because of the binding of ionized calcium to the citrate anticoagulant.

Ionized calcium typically represents approximately 45% of the total plasma concentration. The ionized fraction of calcium changes with pH because calcium and hydrogen ions compete for the binding site on albumin. Acidosis increases ionized calcium, whereas alkalosis reduces ionized calcium.

Calcium Sensitizers

Levosimendan

Levosimendan is the first drug in a novel class of inotropes that increases contractility by increasing the sensitivity of the myocardium to calcium ([Figure 18.12](#)). The inotropic enhancement is a result of binding of levosimendan to troponin C, increasing the sensitivity of troponin to calcium.^{[97,98](#)} Levosimendan also activates adenosine triphosphate-regulated potassium channels,^{[99](#)} causing vasodilation^{[100](#)} and myocardial protection.^{[101](#)} As a result, cardiac output is increased with decreased systemic vascular resistance and pulmonary vascular resistance. Oral bioavailability is 85%. Metabolism is largely hepatic with renal excretion.

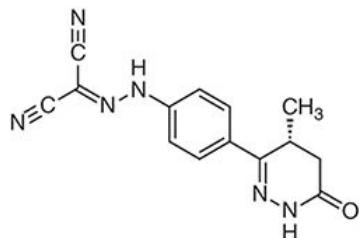


FIGURE 18.12 Levosimendan, the first of a new class of inotropes: calcium sensitizers.

Levosimendan was developed with an indication for the treatment of cardiogenic shock. A reduction in 180-day mortality has not been demonstrated compared to dobutamine in a meta-analysis performed by the Cochrane Collaboration.^{[102](#)} However, a more recent meta-analysis suggested improved survival for patients with chronic heart failure.^{[103](#)} Levosimendan is often considered in situations where conventional therapy for acute severe chronic heart failure is not considered adequate. Levosimendan has also failed to show any benefit in 30-day mortality after cardiac surgery when added to usual care.^{[104](#)} Perioperative levosimendan might reduce the risk of kidney injury following cardiac surgery.^{[105](#)}

Pharmacokinetics

Levosimendan is available as a solution for IV administration. The IV loading dose is 6 to 12 µg/kg given over 10 minutes, followed by an infusion of 0.05 to 2 µg/kg/minute.^{[106](#)} It has a half-life of about 1.5 hours. The clinical effects persist beyond the duration expected from the rapid half-life, likely the result of an active metabolite.^{[107](#)}

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Sympatholytics

Steven E. Miller

α - and β -Adrenergic Receptor Antagonists

α - and β -Adrenergic receptor antagonists prevent the interaction of the endogenous neurotransmitter such as norepinephrine or sympathomimetics with the corresponding adrenergic receptors.¹ Interference with normal adrenergic receptor function attenuates sympathetic nervous system homeostatic mechanisms and evokes predictable pharmacologic responses. Presynaptic agonism of α_2 receptors will result in a similar attenuation of sympathetic outflow by downregulating the release of neurotransmitters to the postsynaptic nerve.

α -Adrenergic Receptor Antagonists

α -Adrenergic receptor antagonists bind selectively to α -adrenergic receptors and interfere with the ability of catecholamines or other sympathomimetics to provoke α -receptor responses. Drug-induced α -adrenergic blockade prevents the effects of catecholamines and sympathomimetics on the heart and peripheral vasculature. The inhibitory action of epinephrine on insulin secretion is prevented. Orthostatic hypotension, baroreceptor-mediated reflex tachycardia, and impotence are invariable side effects of α -adrenergic blockade. Furthermore, absence of β -adrenergic blockade permits maximum expression of cardiac stimulation from norepinephrine, typically leading to tachycardia. These side effects prevent the use of nonselective α -adrenergic antagonists in the management of ambulatory essential hypertension.

Mechanism of Action

Phentolamine, prazosin, and yohimbine are competitive (reversible binding with receptors) α -adrenergic antagonists.² In contrast, phenoxybenzamine binds covalently to α -adrenergic receptors to produce an irreversible and insurmountable type of α -receptor blockade. Once α -blockade has been established with phenoxybenzamine, even massive doses of sympathomimetics are ineffective until the effect of phenoxybenzamine is terminated by metabolism.

Phentolamine and phenoxybenzamine are nonselective α -antagonists acting at postsynaptic α_1 receptors as well as presynaptic α_2 receptors. Prazosin is elective for α_1 receptors, whereas yohimbine is selective for α_2 receptors.

Phentolamine

Phentolamine is a substituted imidazoline derivative that produces transient nonselective α -adrenergic blockade ([Figure 19.1](#)). Administered intravenously (IV), phentolamine produces peripheral vasodilation and a decrease in systemic blood pressure that manifests within 2 minutes and lasts 10 to 15 minutes. This vasodilation reflects α_1 -receptor blockade and a direct action of phentolamine on vascular smooth muscle. Decreases in blood pressure elicit baroreceptor-mediated increases in sympathetic nervous system activity manifesting as cardiac stimulation. In addition to reflex stimulation, phentolamine-induced α_2 -receptor blockade permits enhanced neural release of norepinephrine manifesting as increased heart rate and cardiac output. Indeed, cardiac dysrhythmias and angina pectoris may accompany the administration of phentolamine. Hyperperistalsis, abdominal pain, and diarrhea may be caused by a predominance of parasympathetic nervous system activity. Phentolamine undergoes principally hepatic metabolism and only about 10% of the drug is excreted unchanged in the urine.

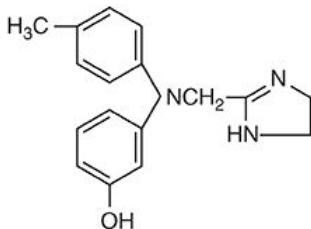


FIGURE 19.1 Phentolamine.

Clinical Uses

The principal use of phentolamine is the treatment of acute hypertensive emergencies, as may accompany intraoperative manipulation of a pheochromocytoma or autonomic nervous system hyperreflexia. Administration of phentolamine, 30 to 70 µg/kg IV (1-5 mg), produces a prompt but transient decrease in systemic blood pressure. A continuous infusion of phentolamine (0.1-2 mg per minute) may be used to maintain normal blood pressure during the intraoperative resection of a pheochromocytoma. Local infiltration with a phentolamine-containing solution (5-15 mg in 10 mL of normal saline) is appropriate when a vasoconstricting sympathomimetic is accidentally administered extravascularly.

Phenoxybenzamine

Phenoxybenzamine is a haloalkylamine derivative that acts as a nonselective α -adrenergic antagonist by combining covalently with α -adrenergic receptors ([Figure 19.2](#)). Blockade at postsynaptic α_1 receptors is more intense than at α_2 receptors.

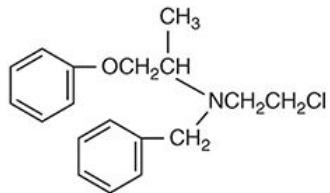


FIGURE 19.2 Phenoxybenzamine.

Pharmacokinetics

Absorption of phenoxybenzamine from the gastrointestinal tract is incomplete. Onset of α -adrenergic blockade is slow, taking up to 60 minutes to reach peak effect even after IV administration. This delay in onset is due to the time required for structural modification of the phenoxybenzamine molecule, which is necessary to render the drug pharmacologically active. The elimination half-time of phenoxybenzamine is about 24 hours, emphasizing the likelihood of cumulative effects with repeated doses.

Cardiovascular Effects

Phenoxybenzamine administered to a supine, normovolemic patient in the absence of increased sympathetic nervous system activity produces little change in systemic blood pressure. Orthostatic hypotension, however, is prominent, especially in the presence of preexisting hypertension or hypovolemia. In addition, impairment of compensatory vasoconstriction results in exaggerated blood pressure decreases in response to blood loss or vasodilating drugs such as volatile anesthetics. Despite decreases in blood pressure, cardiac output is often increased and renal blood flow is not greatly altered unless preexisting renal vasoconstriction is present or significant hypotension results. Cerebral and coronary vascular resistances are nearly unchanged. α -Adrenergic blockade produced by maternal treatment may result in neonatal hypotension and respiratory distress in the first 72 hours of life.³

Noncardiac Effects

Phenoxybenzamine prevents the inhibitory action of epinephrine on the secretion of insulin, but catecholamine-induced glycogenolysis in skeletal muscles or lipolysis is not altered. Stimulation of the radial fibers of the iris is prevented, and miosis is a prominent component of the response to phenoxybenzamine. Sedation may accompany chronic phenoxybenzamine therapy. Nasal stuffiness is due to unopposed vasodilation in mucous membranes in the presence of α -adrenergic blockade and resultant engorgement of the turbinates.

Clinical Uses

Phenoxybenzamine 0.5 to 1.0 mg/kg orally (prazosin is an alternative) is administered preoperatively to control blood pressure in patients with pheochromocytoma. Chronic α -adrenergic blockade, by relieving intense peripheral vasoconstriction, permits expansion of intravascular fluid volume as reflected by a decrease in both hemoglobin and hematocrit. Excessive vasoconstriction with associated tissue ischemia, as accompanies hemorrhagic shock, may be reversed by phenoxybenzamine but only after intravascular fluid volume has been replenished or the resultant hypotension will instead exacerbate the low-flow state.

Treatment of peripheral vascular disease characterized by intermittent claudication is not favorably influenced by α -adrenergic blockade because cutaneous rather than skeletal muscle blood flow is increased. The most beneficial clinical responses to α -adrenergic blockade are in diseases with a large component of cutaneous vasoconstriction, such as Raynaud disease, where smaller arteries that supply blood to skin narrow, limiting blood circulation to affected areas.

Yohimbine

Yohimbine is a selective antagonist at presynaptic α_2 receptors, leading to enhanced release of norepinephrine from nerve endings. As a result, this drug may be useful in the treatment of the rare patient suffering from idiopathic orthostatic hypotension. In the past, yohimbine has been used in male patients suffering from erectile dysfunction or impotence resulting from vascular, diabetic, or psychogenic origins. Yohimbine readily crosses the blood-brain barrier and may be associated with increased skeletal muscle activity and tremor. Excessive doses of yohimbine may produce tachycardia, hypertension, rhinorrhea, paresthesias, and dissociative states. Observations that α_2 -adrenergic agonists can decrease anesthetic requirements by actions on presynaptic α_2 receptors in the central nervous system (CNS) suggest a possible interaction of yohimbine with volatile anesthetics.⁴

Doxazosin

Doxazosin is approved for both treatment of hypertension and benign prostatic hypertrophy (BPH). It is a selective postsynaptic α_1 -receptor antagonist that is 65% bioavailable with oral administration. Peak levels of doxazosin are seen 2 to 3 hours following oral administration and effectively relaxes prostatic and vascular smooth muscle. Doxazosin is primarily metabolized in the liver by O-demethylation and excreted in the feces. The terminal elimination life of doxazosin is 22 hours and is recommended as a single daily dose in the morning.

Prazosin

Prazosin is a selective postsynaptic α_1 -receptor antagonist that leaves intact the inhibiting effect of α_2 -receptor activity on norepinephrine release from nerve endings. As a result, prazosin is less likely than nonselective α -adrenergic antagonists to evoke reflex tachycardia. Prazosin dilates both arterioles and veins. Following oral administration, the onset of action is approximately 30 minutes and the duration of action is about 4 to 6 hours. Elimination of prazosin is principally by hepatic metabolism.

Terazosin

α -Blocker therapy of BPH is based on α_1 -mediated innervation of prostatic smooth muscle that controls contraction of the prostate and obstruction of the bladder outlet. Terazosin is a long-acting, orally effective

α_1 -adrenergic antagonist that may be useful in the treatment of benign prostatic hyperplasia by virtue of its ability to relax prostatic smooth muscle.

Tamsulosin

Tamsulosin is an orally effective α_{1a} -adrenergic antagonist that is indicated for the treatment of the signs and symptoms of BPH. Side effects may include orthostatic hypotension, vertigo, and syncope. Tamsulosin also has a noninsignificant risk of sexual side effects including ejaculatory dysfunction. The clearance of tamsulosin is decreased in the presence of cimetidine.

Alfuzosin

Alfuzosin is also a selective inhibitor of α_{1a} -adrenergic receptors and has been used to treat BPH specifically in younger populations. Unlike tamsulosin, sexual side effects seem to be much less common without a decrease in prostatic relaxation ability. Side effects of alfuzosin include dizziness and systemic hypotension with reflex tachycardia. Alfuzosin undergoes extensive liver metabolism by multiple mechanisms into inactive metabolites that are then excreted nearly 3:1 in the bile; only 11% remains unchanged and is excreted by the kidneys.

Sildosin

Sildosin is a very selective α_{1a} -adrenergic receptor antagonist with more prostate specific activity and less systemic side effects than other drugs for the treatment of BPH.⁵ It has very rapid oral absorption but is only 32% bioavailable. It is processed by two different hepatic pathways, and the primary metabolite is active but with only 50% of the parent compound's activity. The metabolite's are excreted in the 3:2 hepatically versus renally.

Tolazoline

Tolazoline is a competitive nonselective α -adrenergic receptor antagonist. This drug has been used to treat persistent pulmonary hypertension of the newborn, but its use for this purpose has been largely replaced by nitric oxide. Side effects of tolazoline include systemic hypotension with reflex tachycardia, cardiac dysrhythmias, and pulmonary and gastrointestinal hemorrhages. Tolazoline is excreted mainly unchanged by the kidneys.

α_2 -Adrenergic Receptor Agonists

α_2 -Adrenergic receptor agonists bind selectively to presynaptic α_2 -adrenergic receptors and, by a negative feedback mechanism, decrease the release of norepinephrine from presynaptic nerve terminals and reduce sympathetic outflow with similar decreases in blood pressure as α_1 antagonists. Most α_2 receptors are found in the CNS, especially in the brainstem and the locus ceruleus. Peripheral inhibition of α_2 receptors can result in inhibition of insulin release and induction of glucagon from the pancreas. Clinical pharmacologic effects include hypotension, bradycardia, and central sedation with some mild effects of analgesia all related to the sympatholytic effects.

Mechanism of Action

α_2 -Adrenergic receptor agonists have selective affinity for α_2 -adrenergic receptors and act competitively. Binding of α_2 agonists can be displaced from binding sites in the CNS resulting in reversal of the CNS effects. Withdrawal after even short-term use can result in a rebound effect with a dramatic increase in sympathetic outflow causing elevations in heart rate and hypertension to even dangerous levels.

Clonidine

Administration results in dose-dependent decreases in heart rate and blood pressure and is used clinically to treat resistant hypertension, tremors from central stimulant medications, and opioid withdrawal.⁶ Clonidine is

a partial agonist of α_2 receptors with a 400:1 α_2 - α_1 receptor preference. Clonidine is available in an IV, oral, and transdermal preparation and is metabolized in the liver but is excreted mostly unchanged in the urine and to a lesser extent in the bile and feces. Terminal half-life is approximately 12 to 16 hours but can be extremely variable with any liver or kidney dysfunction.

Dexmedetomidine

Dexmedetomidine is a selective α_2 agonist with a 1,600:1 preference for α_2 -receptors. It is IV administered as an infusion from 0.1 to 1.5 $\mu\text{g}/\text{kg}$ per minute with a terminal elimination half-life of 2 hours. Most often, this α_2 agonist is used in the intensive care and operating room settings as a sedative and analgesic due to its central sympatholytic effects. Dexmedetomidine undergoes extensive biotransformation in the liver and is excreted mostly in the urine; liver impairment can dramatically increase plasma levels and duration of action due to significantly decreased metabolism during infusion. Its potent binding and short half-life can induce physiologic dependence and result in the aforementioned withdrawal phenomenon after only days of administration resulting in tachycardia, hypertension, and anxiety. Interestingly, large IV boluses (0.25-1 $\mu\text{g}/\text{kg}$ over 3-5 minutes) result in a paradoxical hypertension with a decrease in heart rate and resembles phenylephrine as a resultant effect of crossover α_1 stimulation.

β -Adrenergic Receptor Antagonists

β -Adrenergic receptor antagonists bind selectively to β -adrenergic receptors and interfere with the ability of catecholamines or other sympathomimetics to provoke β responses. Drug-induced β -adrenergic blockade prevents the effects of catecholamines and sympathomimetics on the heart and the smooth muscles of the airways and blood vessels. β -Antagonist therapy should be continued throughout the perioperative period to maintain desirable drug effects and to avoid the risk of sympathetic nervous system hyperactivity (rebound) associated with abrupt discontinuation of these drugs. Propranolol is the standard β -adrenergic antagonist drug to which all other β -adrenergic antagonists are commonly compared.

Mechanism of Action

β -Adrenergic receptor antagonists exhibit selective affinity for β -adrenergic receptors where they act by competitive inhibition. Binding of antagonist drugs to β -adrenergic receptors is reversible such that the drug can be displaced from the occupied receptors if sufficiently large amounts of agonist become available. Competitive antagonism causes a rightward displacement of the dose-response curve for the agonist, but the slope of the curve remains unchanged, emphasizing that sufficiently large doses of the agonist may still exert a full pharmacologic effect. Chronic administration of β -adrenergic antagonists is associated with an increase in the number of β -adrenergic receptors and an eventual need to uptitrate medication doses to maintain the same pharmacologic effects.

β -Adrenergic receptors are G protein-coupled receptors and their occupancy by agonists (norepinephrine, epinephrine) stimulates G proteins that in turn activate adenylyl cyclase to produce cyclic adenosine monophosphate (cAMP). Protein kinases are activated by cAMP, which in turn phosphorylate proteins including L-type voltage-dependent calcium channels and troponin C in a variety of tissues (especially myocardium). The net effect of β -adrenergic stimulation in the heart is to produce positive chronotropic, inotropic, and dromotropic effects along with a negative lusitropic effect and inadvertent positive bathmotropy. These are the responses that are blunted by β -adrenergic receptor antagonists and it is estimated that about 75% of β receptors in the myocardium are β_1 , whereas β_2 receptors account for about 20% of β receptors.

Structure-Activity Relationships

β -Adrenergic antagonists are derivatives of the β agonist drug isoproterenol ([Figure 19.3](#)). Substitutions on the benzene ring determine whether the drug acts on β -adrenergic receptors as an antagonist or agonist. The levorotatory forms of β antagonists and agonists are more potent than the dextrorotatory forms. For example,

the dextrorotatory isomer of propranolol has less than 1% of the potency of the levorotatory isomer for blocking β -adrenergic receptors.

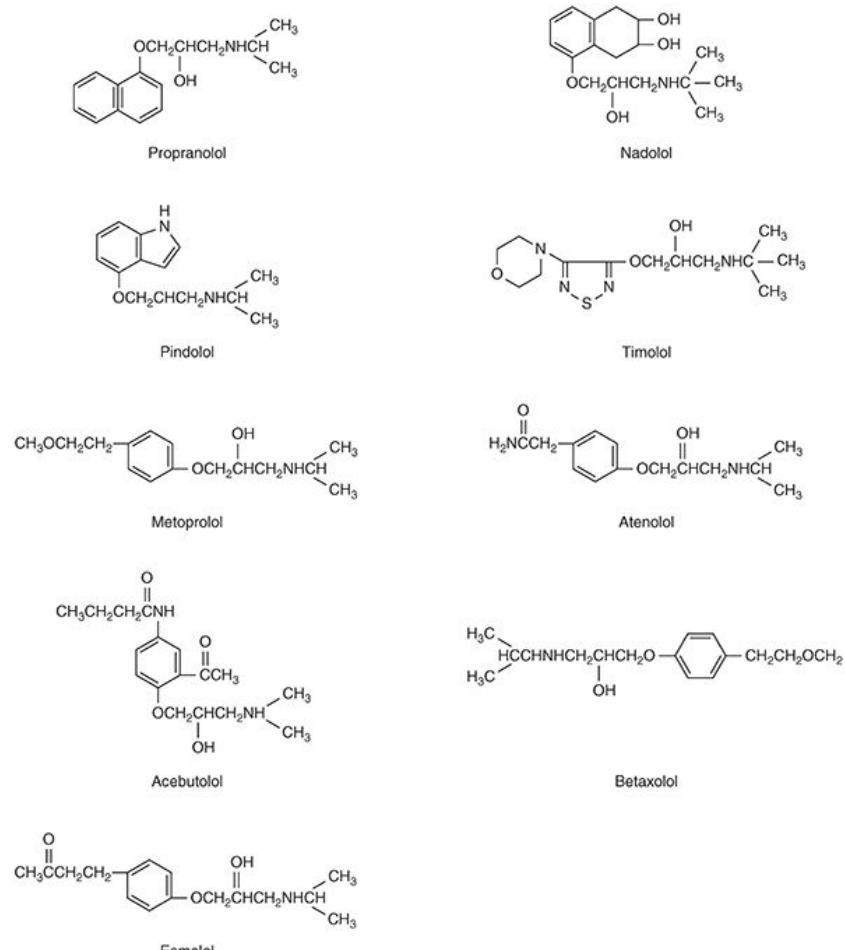


FIGURE 19.3 β -Adrenergic antagonists.

Classification

β -Adrenergic receptor antagonists are classified as nonselective for β_1 and β_2 receptors (propranolol, nadolol, timolol, pindolol) and cardioselective (metoprolol, atenolol, acebutolol, betaxolol, esmolol, bisoprolol, nebivolol) for β_1 receptors ([Tables 19.1](#) and [19.2](#)). It is important to recognize that β -receptor selectivity is dose dependent and is lost when large doses of an antagonist are administered. This emphasizes that selectivity should not be interpreted as specificity for a specific type of β -adrenergic receptor. β -Adrenergic antagonists are further classified as partial or pure antagonists on the basis of the presence or absence of intrinsic sympathomimetic activity (see [Tables 19.1](#) and [19.2](#)). Drugs that exhibit cardiac selectivity for β_1 receptors (cardioselective) are better suited for administration to patients with asthma and reactive airway disease. Theoretically, cardioselective drugs are better suited for treatment of patients with essential hypertension because these drugs lack inhibition of peripheral β_2 receptors that produce vasodilation.

TABLE 19.1

Comparative characteristics of β -adrenergic receptor antagonists

	Propranolol	Nadolol	Pindolol	Timolol	Metoprolol	Atenolol	Acebutolol	Betaxolol	Esmolol	Nebivolol
Cardiac selectivity	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes

Partial agonist activity	No	No	Yes	No	No	No	Yes	No	No	No
Protein binding (%)	90-95	30	40-60	10	10	5	25		55	98
Clearance	Hepatic	Renal	Hepatic Renal	Hepatic	Hepatic	Renal	Hepatic Renal	Hepatic Renal	Plasma hydrolysis	Hepatic
Active metabolites	Yes	No	No	No	No	No	Yes		No	Yes
Elimination half-time (hours)	2-3	20-24	3-4	3-4	3-4	6-7	3-4	11-22	0.15	12-19
First-pass hepatic metabolism (estimate) (%)	75	Minimal	10-15	50	60	10	60	11-16	--*	12-96
Blood level variability	++++	+	++	+++	+++	+	++	+	--*	+++
Adult oral dose (mg)	40-360	40-320	5-20	10-30	50-400	50-200	200-800	10-20		5-40
Adult intravenous (IV) dose (mg)	1-10		0.4-2	0.4-1	1-15	5-10	12.5-50		10-80 IV 50-300 µg/kg/minute	

Abbreviations: +, minimal; ++, modest; +++, moderate; +++, marked; *, only available intravenously.

TABLE 19.2

Comparative characteristics of β-adrenergic receptor antagonists effective in the treatment of congestive heart failure

	Metoprolol (extended release)	Carvedilol	Bisoprolol
Cardiac selectivity	Yes	No	Yes
Partial agonist activity	No	No	No
Initial oral dose ^a	6.25 mg twice daily	3.125 mg twice daily	1.25 mg daily
Desired dosage range ^a	50-150 mg daily	25-50 mg twice daily	5 mg daily

^aRecommended doses for treatment of patients with mild to moderate congestive heart failure.

β₁-Receptor blockade is associated with slowing of the sinus rate, slowing of conduction of cardiac impulses through the atrioventricular node, a decrease in inotropy, an increase in lusitropy, and usually a decrease in bathmotropy. These effects are relatively greater during activity than during rest. The result is a decrease in myocardial oxygen demand with a subsequent decrease in the occurrence of myocardial ischemia during exercise. The decrease in heart rate also increases diastolic perfusion time, which may enhance myocardial perfusion. β₂-Receptor blockade increases the risk of bronchospasm in patients with reactive airway disease and may worsen the clinical symptoms of peripheral vascular disease.

β-Adrenergic antagonists may produce some degree of membrane stabilization in the heart (inhibition of propagation of action potentials across the cell membrane similar to sodium channel blockers that are class I antiarrhythmic) and thus resemble quinidine. This membrane stabilization effect, however, is detectable only at plasma concentrations that are far higher than needed to produce clinically adequate β-adrenergic blockade.

Pharmacokinetics

The principal difference in pharmacokinetics between all the β-adrenergic receptor antagonists is the elimination half-time ranging from brief for esmolol (about 10 minutes) to hours for the other drugs (see **Table 19.1**). Elimination half-time is considered in the perioperative period when redosing intervals are being

developed or when conversion to another β -adrenergic receptor drug is planned. Among the β -adrenergic receptor antagonists, only propranolol and nebivolol are highly protein bound. The volume of distribution of these drugs is high, and they are rapidly distributed following IV administration.

β -Adrenergic receptor antagonists are eliminated by several different pathways, and this must be considered in the presence of renal and/or hepatic dysfunction (see [Table 19.1](#)). The therapeutic plasma concentration varies greatly among these drugs and between patients (interpatient variability). Explanations for interpatient variability include differences in basal sympathetic nervous system tone, flat dose-response curves for the drug so changes in plasma concentrations evoke minimal changes in pharmacologic effects, impact of active metabolites, and genetic differences in β -adrenergic receptors that influence how an individual patient responds to a given drug and plasma concentration.

Propranolol

Propranolol is a nonselective β -adrenergic receptor antagonist that lacks intrinsic sympathomimetic activity and thus is a pure antagonist (see [Table 19.1](#)). Antagonism of β_1 and β_2 receptors produced by propranolol is about equal. As the first β -adrenergic antagonist introduced clinically, propranolol is usually the standard drug to which β -adrenergic antagonists are compared. Typically, propranolol is administered in stepwise increments until physiologic plasma concentrations have been attained, as indicated by a resting heart rate of 55 to 60 beats per minute.

Cardiac Effects

The most important pharmacologic effects of propranolol are on the heart. Because of β_1 -receptor blockade, propranolol decreases heart rate and myocardial contractility, resulting in decreased cardiac output. These effects on heart rate and cardiac output are especially prominent during exercise or in the presence of increased sympathetic nervous system activity. Heart rate slowing induced by propranolol lasts longer than the negative inotropic effects, suggesting a possible subdivision of β_1 receptors. Concomitant blockade of β_2 receptors by propranolol increases peripheral vascular resistance, including coronary vascular resistance. Although prolongation of systolic ejection and dilatation of the cardiac ventricles caused by propranolol increases myocardial oxygen requirements, the oxygen-sparing effects of decreased heart rate and myocardial contractility predominate. As a result, propranolol may relieve myocardial ischemia, even though drug-induced increases in coronary vascular resistance oppose coronary blood flow. Sodium retention associated with propranolol therapy most likely results from intrarenal hemodynamic changes that accompany drug-induced decreases in cardiac output.

Pharmacokinetics

Propranolol is rapidly and almost completely absorbed from the gastrointestinal tract, but systemic availability of the drug is limited by extensive hepatic first-pass metabolism, which may account for 90% to 95% of the absorbed dose. There is considerable individual variation in the magnitude of hepatic first-pass metabolism, accounting for up to 20-fold differences in plasma concentrations of propranolol in patients after oral administration of comparable doses.⁷ Hepatic first-pass metabolism is the reason the oral dose of propranolol (40-800 mg per day) must be substantially greater than the IV dose (0.05 mg/kg given in increments of 0.5-1.0 mg every 5 minutes). Propranolol is not effective when administered intramuscularly.

Protein Binding

Propranolol is extensively bound (90%-95%) to plasma proteins. Heparin-induced increases in plasma concentrations of free fatty acids due to increased lipoprotein lipase activity result in decreased plasma protein binding of propranolol ([Figure 19.4](#)).⁸ In addition, hemodilution that occurs when cardiopulmonary bypass is initiated may alter protein binding of drugs because of the nonphysiologic protein concentration in the pump prime.

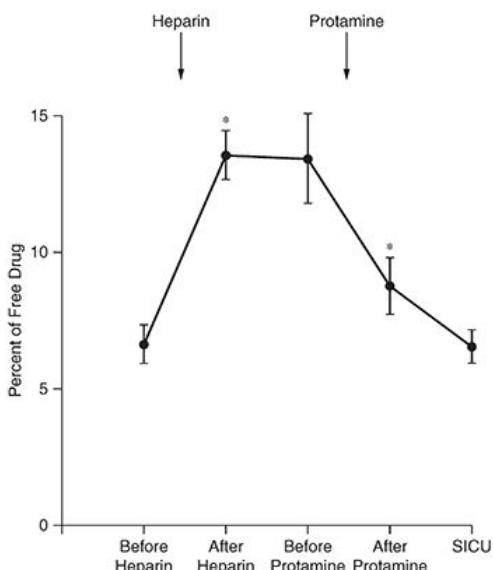


FIGURE 19.4 Heparin administration is associated with decreased plasma protein binding of propranolol manifesting as an increased plasma concentration of free (unbound) drug. (Mean \pm standard error; $*P < .05$.) Abbreviation: SICU, surgical intensive care unit. Reprinted with permission from Wood M, Shand DG, Wood AJ. Propranolol binding in plasma during cardiopulmonary bypass. Anesthesiology. 1979;51(6):512-516. Copyright © 1979 American Society of Anesthesiologists, Inc.

Metabolism

Clearance of propranolol from the plasma is by hepatic metabolism. An active metabolite, 4-hydroxypropranolol, is detectable in the plasma after oral administration of propranolol. Indeed, cardiac β -blocking activity after equivalent doses of propranolol is greater after oral than after IV administration, presumably reflecting the effects of this metabolite, which is equivalent in activity to the parent compound. The elimination half-time of propranolol is 2 to 3 hours, whereas that of 4-hydroxypropranolol is even briefer. The plasma concentration of propranolol or the total dose does not correlate with its therapeutic effects. Furthermore, the assay for propranolol may not detect 4-hydroxypropranolol.

Elimination of propranolol is greatly decreased when hepatic blood flow decreases. In this regard, propranolol may decrease its own clearance rate by decreasing cardiac output and hepatic blood flow. Alterations in hepatic enzyme activity may also influence the rate of hepatic metabolism. Renal failure does not alter the elimination half-time of propranolol, but accumulation of metabolites may occur.

Clearance of Local Anesthetics

Propranolol decreases clearance of amide local anesthetics by decreasing hepatic blood flow and inhibiting metabolism in the liver.⁹ For example, in humans, propranolol causes clearance to be decreased to a much greater extent (46%) than would be predicted from a maximum 25% decrease in hepatic blood flow, implying that drug metabolism in the liver has also been affected.¹⁰ Bupivacaine clearance is relatively insensitive to changes in hepatic blood flow (low-extraction drug), suggesting that the 35% decrease in clearance of this local anesthetic reflects propranolol-induced decreases in metabolism (Figure 19.5).⁹ Because clearance of drugs with low extraction ratios is inversely related to plasma protein binding, an increase in bupivacaine binding to α_1 -acid glycoprotein (responsible for 90% binding of bupivacaine) caused by propranolol could explain a decrease in clearance. Nevertheless, propranolol does not alter α_1 -acid glycoprotein concentrations.¹⁰ It is conceivable that systemic toxicity of bupivacaine could be increased by propranolol and presumably other β antagonists that interfere with the clearance of this and other amide local anesthetics. It has also been demonstrated that propranolol pretreatment can result in increased concentration of mepivacaine serum concentrations.¹¹

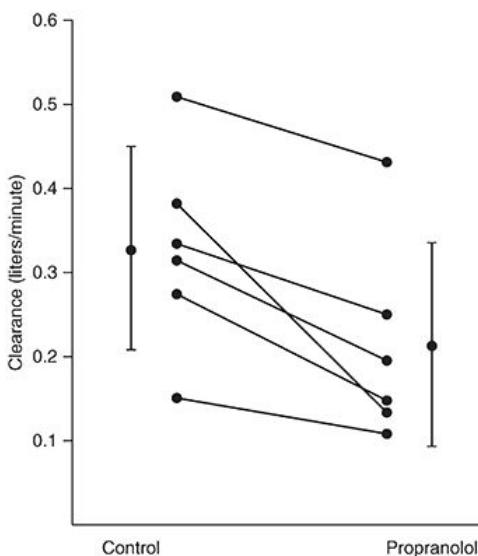


FIGURE 19.5 Bupivacaine clearance is decreased 35% in subjects treated with propranolol compared with control measurements. Reprinted with permission from Bowdle TA, Freund PR, Slattery JT. Propranolol reduces bupivacaine clearance. *Anesthesiology*. 1987;66(1):36-38. Copyright © 1987 American Society of Anesthesiologists, Inc.

Clearance of Opioids

Pulmonary first-pass uptake of fentanyl is substantially decreased in patients being treated chronically with propranolol.¹² As a result, 2 to 4 times as much injected fentanyl enters the systemic circulation in the time period immediately after injection. This response most likely reflects the ability of one basic lipophilic amine (propranolol) to inhibit the pulmonary uptake of a second basic lipophilic amine (fentanyl).

Nadolol and Pindolol

Nadolol and pindolol are nonselective β -adrenergic receptor antagonists; nadolol is unique in that its long duration of action permits once daily administration.

Pharmacokinetics

Nadolol is slowly and incompletely absorbed (an estimated 30%) from the gastrointestinal tract. Metabolism does not occur, with about 75% of the drug being excreted unchanged in urine and the remainder in bile. Therefore, wide individual variations in plasma concentrations that occur with nadolol cannot be attributed to differences in metabolism, as occur with propranolol. The elimination half-time is 20 to 40 hours, accounting for the need to administer this drug only once a day. The elimination half-time of pindolol is 3 to 4 hours, and this is increased to longer than 11 hours in patients with renal failure.

Timolol

Timolol is a nonselective β -adrenergic receptor antagonist that is as effective as propranolol for various therapeutic indications. In addition, timolol is effective in the treatment of glaucoma because of its ability to decrease intraocular pressure, presumably by decreasing the production of aqueous humor. Timolol is administered as eyedrops in the treatment of glaucoma, but systemic absorption may be sufficient to cause resting bradycardia and increased airway resistance. Indeed, bradycardia and hypotension that are refractory to treatment with atropine have been observed during anesthesia in pediatric and adult patients receiving topical timolol with or without pilocarpine.¹³ Timolol may be associated with impaired control of ventilation in neonates, resulting in unexpected postoperative apnea.¹⁴ Immaturity of the neonate's blood-brain barrier may facilitate access of this drug to the CNS.

Pharmacokinetics

Timolol is rapidly and almost completely absorbed after oral administration. Nevertheless, extensive first-pass hepatic metabolism limits the amount of drug reaching the systemic circulation to about 50% of that absorbed from the gastrointestinal tract. Protein binding of timolol is not extensive. The elimination half-time is about 4 hours.

Metoprolol

Metoprolol is a selective β_1 -adrenergic receptor antagonist that prevents inotropic and chronotropic responses to β -adrenergic stimulation. Conversely, bronchodilator, vasodilator, and metabolic effects of β_2 receptors remain intact such that metoprolol is less likely to cause adverse effects in patients with chronic obstructive airway disease or peripheral vascular disease and in patients vulnerable to hypoglycemia. It is important to recognize, however, that selectivity is dose related, and large doses of metoprolol are likely to become nonselective, exerting antagonist effects at β_2 receptors as well as β_1 receptors. Indeed, airway resistance may increase in asthmatic patients treated with metoprolol, although the magnitude of increase will be less than that evoked by propranolol. Furthermore, metoprolol-induced increases in airway resistance are more readily reversed with β_2 -adrenergic agonists such as terbutaline.

Pharmacokinetics

Metoprolol is readily absorbed from the gastrointestinal tract, but this is offset by substantial hepatic first-pass metabolism such that only about 40% of the drug reaches the systemic circulation. Protein binding is low; it is estimated to account for about 10% of the drug. None of the hepatic metabolites have been identified as active. A small amount (<10%) of the drug appears unchanged in urine. There are two available oral formulation of metoprolol: metoprolol tartrate and metoprolol succinate. The elimination half-time of metoprolol tartrate is 2 to 3 hours and correlates to a need for at least a twice daily dosing strategy with a 3 or 4 times daily strategy providing a more reliable control of heart rate. Metoprolol succinate results in a significantly extended time to peak concentrations and overall decreased plasma concentrations compared to metoprolol tartrate at equal daily doses. Metoprolol succinate elimination half-time is 5 to 7 hours and can be used in once daily dosing regimens but in some patients can still result in β -blocker withdrawal tachycardia at 24 hours necessitating twice daily dosing. Overall, plasma concentrations of metoprolol do not correlate with therapeutic effects of the drug.

Atenolol

Atenolol is an even more selective β_1 -adrenergic antagonist that may have specific value in patients in whom the continued presence of β_2 -receptor activity is desirable. In patients at risk for coronary artery disease who must undergo noncardiac surgery, treatment with IV atenolol before and immediately after surgery, followed by oral therapy during the remainder of the hospitalization, decreases mortality and the incidence of cardiovascular complications for as long as 2 years.¹⁵ Perioperative administration of atenolol to patients at high risk for coronary artery disease significantly decreases the incidence of postoperative myocardial ischemia.¹⁶

The antihypertensive effect of atenolol is prolonged, permitting this drug to be administered once daily for the treatment of hypertension. Like nadolol, atenolol does not enter the CNS in large amounts, but fatigue and mental depression still occur. Unlike nonselective β -adrenergic antagonists, atenolol does not appear to potentiate insulin-induced hypoglycemia and can thus be administered with caution to patients with diabetes mellitus whose hypertension is not controlled by other antihypertensives.

Pharmacokinetics

About 50% of an orally administered dose of atenolol is absorbed from the gastrointestinal tract, with peak concentrations occurring 1 to 2 hours after oral administration. Atenolol undergoes little or no hepatic metabolism and is eliminated principally by renal excretion. The elimination half-time is 6 to 7 hours; this may increase to more than 24 hours in patients with renal failure.

Betaxolol

Betaxolol is a cardioselective β_1 -adrenergic antagonist with no intrinsic sympathomimetic activity and weak membrane-stabilizing activity. High doses can be expected to produce some β_2 -adrenergic antagonist effects on bronchial and vascular smooth muscle. Absorption after an oral dose is nearly complete. Its elimination half-time is 11 to 22 hours, making it one of the longest acting β -adrenergic antagonists. Clearance is primarily by metabolism, with renal elimination contributing less to overall removal of the drug from the plasma. A single oral dose daily is useful for the treatment of hypertension. A topical preparation is used as an alternative to timolol for treatment of chronic open-angle glaucoma. The risk of bronchoconstriction in patients with airway hyperreactivity may be less with betaxolol than with timolol.

Bisoprolol

Bisoprolol is one of the most β_1 -selective antagonist drugs, and it does not have any significant intrinsic agonist activity. The elimination half-time is 9 to 12 hours. Bisoprolol is eliminated equally by renal and nonrenal mechanisms. Metabolites are pharmacologically inactive. The most prominent pharmacologic effect of bisoprolol is a negative chronotropic effect. Bisoprolol is useful in the treatment of essential hypertension and has been shown to improve survival in patients with mild to moderate congestive heart failure (see [Table 19.2](#)).

Nebivolol

Nebivolol is a very potent and most selective β_1 -antagonist drug¹⁷ listed thus far as it is 3.5 times more selective than bisoprolol¹⁸ and also does not have any significant intrinsic agonist activity. Above doses of 10 mg, or in those patients with certain cytochrome P450 polymorphisms, nebivolol can exhibit low β_2 antagonism as well. With an elimination half-time of 12 to 19 hours, it is a once daily regimen that allows accidental delay in subsequent doses without withdrawal. Nebivolol is equally eliminated in the urine unchanged and in the feces as an inactive metabolite. At this time, nebivolol is only currently approved for the treatment of essential hypertension.

Esmolol

Esmolol is a rapid-onset and short-acting selective β_1 -adrenergic receptor antagonist that is administered only IV (see [Figure 19.3](#)). After a typical initial dose of 0.5 mg/kg IV over about 60 seconds, the full therapeutic effect is evident within 5 minutes, and its action ceases within 10 to 30 minutes after administration is discontinued. These characteristics make esmolol a useful drug for preventing or treating adverse systemic blood pressure and heart rate increases that occur intraoperatively in response to noxious stimulation, as during tracheal intubation. For example, esmolol, 150 mg IV, administered about 2 minutes before direct laryngoscopy and tracheal intubation provides reliable protection against increases in both heart rate and systolic blood pressure, which predictably accompanies tracheal intubation ([Figure 19.6](#)).¹⁹

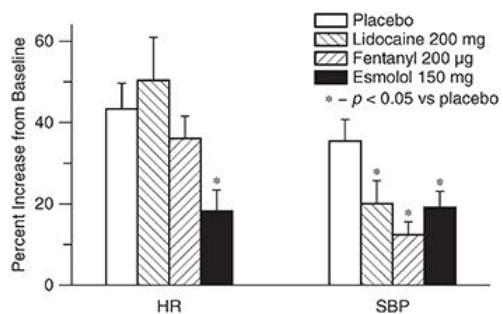


FIGURE 19.6 Maximum percent increases in heart rate (HR) and systolic blood pressure (SBP) after induction of anesthesia and direct laryngoscopy with tracheal intubation in patients pretreated with saline, lidocaine, fentanyl, or esmolol. All three drugs blunt the increase in SBP, but only esmolol is also effective in attenuating the increase in HR. *Reprinted with permission from Helfman SM, Gold MI, DeLisser EA, et al.*

Which drug prevents tachycardia and hypertension associated with tracheal intubation: lidocaine, fentanyl, or esmolol? Anesth Analg. 1991;72(4):482-486. Copyright © 1991 International Anesthesia Research Society.

Lidocaine or fentanyl is effective in blunting the increase in systolic blood pressure associated with laryngoscopy and tracheal intubation, but heart rate is not influenced (see [Figure 19.6](#)).¹⁹ Other reports describe prevention of perioperative tachycardia and hypertension with esmolol, 100 to 200 mg IV, administered over 15 seconds before the induction of anesthesia.^{20,21} Prior administration of esmolol, 500 µg/kg per minute IV, to patients undergoing electroconvulsive therapy with anesthesia induced by methohexitol plus succinylcholine results in attenuation of the heart rate increase and a decrease in the length of the electrically induced seizures.²² Esmolol has been used during resection of pheochromocytomas and may be useful in the perioperative management of thyrotoxicosis, pregnancy-induced hypertension, and epinephrine- or cocaine-induced cardiovascular toxicity.²³⁻²⁷ Detrimental effects of catecholamine release during anesthesia in patients with hypertrophic obstructive cardiomyopathy and in patients experiencing hypercyanotic spells associated with tetralogy of Fallot may be blunted by administration of esmolol.²⁸

Conversely, treatment of excessive sympathetic nervous system activity produced by cocaine or systemic absorption of topical or subcutaneous epinephrine with β-adrenergic receptor antagonists has been associated with fulminant pulmonary edema and irreversible cardiovascular collapse.²⁹ It is possible that acute drug-induced β-receptor antagonism removes the ability of the heart to increase heart rate and myocardial contractility to compensate for catecholamine-induced increases in left ventricular afterload. In this regard, persistent symptomatic systemic hypertension owing to catecholamine-induced sympathetic nervous system stimulation is more safely treated with a peripheral vasodilator drug such as sodium nitroprusside or nitroglycerin.

The β₁ selectivity of esmolol may unmask β₂-mediated vasodilation by epinephrine or epinephrine-secreting tumors.³⁰ Administration of esmolol to patients chronically treated with β-adrenergic antagonists has not been observed to produce additional negative inotropic effects.³¹ The presumed mechanism for this observation is that esmolol, in the dose used, does not occupy sufficient additional β receptors to produce detectable increases in β-blockade. Likewise, esmolol infused during cardiopulmonary bypass is not associated with adverse effects after discontinuation of cardiopulmonary bypass.³²

Esmolol (1 mg/kg IV followed by 250 µg/kg per minute IV) significantly decreases the plasma concentration of propofol required to prevent patient movement in response to a surgical skin incision.³³ This effect does not seem to be explained by a pharmacokinetic interaction between the two drugs.

Pharmacokinetics

Esmolol is available for IV administration only. The only other β-adrenergic antagonists that may be administered IV are propranolol and metoprolol. The commercial preparation of esmolol is buffered to pH 4.5 to 5.5, which may be one of the factors responsible for pain on injection. The drug is compatible with commonly used IV solutions and nondepolarizing neuromuscular blocking drugs. The elimination half-time of esmolol is about 9 minutes, reflecting its rapid hydrolysis in the blood by plasma esterases that is independent of renal and hepatic function.³⁴ Less than 1% of the drug is excreted unchanged in urine, and about 75% is recovered as an inactive acid metabolite. Clinically insignificant amounts of methanol also occur from the hydrolysis of esmolol. Plasma esterases responsible for the hydrolysis of esmolol are distinct from plasma cholinesterase, and the duration of action of succinylcholine is not predictably prolonged in patients treated with esmolol.³⁵ Evidence of the short duration of action of esmolol is return of the heart rate to predrug levels within 15 minutes after discontinuing the drug. Indeed, plasma concentrations of esmolol are usually not detectable 15 minutes after discontinuing the drug. Poor lipid solubility limits transfer of esmolol into the CNS or across the placenta.²⁴

Class-Related Side Effects

The side effects of β -adrenergic antagonists are similar for all available drugs, although the magnitude may differ depending on their selectivity and the presence or absence of intrinsic sympathomimetic activity. β -Adrenergic antagonists exert their most prominent pharmacologic effects as well as side effects on the cardiovascular system. These drugs may also alter airway resistance, carbohydrate and lipid metabolism, and the distribution of extracellular ions. β -Adrenergic antagonists may cause hypoglycemia.³⁶ Additive effects between drugs used for anesthesia and β -adrenergic antagonists may occur including sedation, bradycardia, and hypotension. Many β -Adrenergic antagonists penetrate the blood–brain barrier and cross the placenta. Gastrointestinal side effects include nausea, vomiting, and diarrhea. Fever, rash, myopathy, alopecia, and thrombocytopenia have been associated with chronic β -adrenergic antagonist treatment. β -Adrenergic antagonists have been reported to decrease plasma concentrations of high-density lipoproteins and to increase triglyceride and uric acid levels.

The principal contraindication to administration of β -adrenergic antagonists is preexisting atrioventricular heart block or acute cardiac failure not caused by tachycardia, despite being a mainstay of medical therapy for chronic congestive heart failure. Administration of β -adrenergic antagonists to hypovolemic patients with compensatory tachycardia has been known to produce profound and resistant hypotension.³⁷ Nonselective β -adrenergic antagonists or high doses of selective β -adrenergic antagonists are not recommended for administration to patients with any diagnosis of reactive or obstructive airway disease. In patients with diabetes mellitus, there is the risk that β -adrenergic blockade may mask the signs of hypo- or hyperglycemia and thus delay clinical recognition.

Cardiovascular System

β -Adrenergic antagonists produce negative inotropic and chronotropic effects. In addition, the conduction speed (dromotropy) of cardiac impulses through the atrioventricular node is slowed, and the rate of spontaneous phase 4 depolarization is decreased. Preexisting atrioventricular heart block due to any cause will likely be accentuated by β -adrenergic antagonists.

The cardiovascular effects of β -adrenergic blockade reflect removal of sympathetic nervous system innervation to the heart (β_1 -blockade) and not membrane stabilization, which occurs only at high plasma concentrations of the antagonist drug. In addition, nonselective β -adrenergic blockade resulting in β_2 -adrenergic receptor antagonism may impede left ventricular ejection due to unopposed α -adrenergic receptor-mediated peripheral vasoconstriction. The magnitude of cardiovascular effects produced by β -adrenergic antagonists is greatest when preexisting sympathetic nervous system activity is increased, as during exercise or in patients in cardiac failure. Indeed, the tachycardia of exercise is consistently attenuated by β -adrenergic antagonists, and age adjusted maximal heart rate should be further adjusted down 10 beats per minute. Furthermore, new or high dose administration of a β antagonist may precipitate cardiac failure in a patient who was previously compensated. Resting bradycardia is minimized, and cardiac failure is less likely to occur when a partial β -adrenergic antagonist with intrinsic sympathomimetic activity is administered. Acute cardiac failure is rare with oral administration of β -adrenergic antagonists.

Classically, β -adrenergic antagonists prevent inotropic and chronotropic effects of isoproterenol as well as baroreceptor-mediated increases in heart rate evoked by decreases in systemic blood pressure in response to peripheral vasodilator drugs. Conversely, the influence of β -adrenergic antagonists on the cardiac-stimulating effects of calcium, glucagon, and digitalis preparations is not detectable. Likewise, β -adrenergic antagonists do not alter the response to α -adrenergic agonists such as epinephrine or phenylephrine. In theory, the pressor effect of epinephrine is enhanced because the nonselective β antagonists prevent the β_2 vasodilation of epinephrine and leaves unopposed α -adrenergic effects to predominate. The presence of unopposed α -adrenergic-induced vasoconstriction, as might be seen if propranolol were given to a patient acutely intoxicated with cocaine, will likely provoke paradoxical hypertension and may even precipitate cardiac failure in the presence of diseased myocardium that cannot respond to sympathetic nervous system stimulation because of β -adrenergic blockade.³⁸ Unexpected hypertension has occurred in patients receiving clonidine who subsequently receive a nonselective β -adrenergic antagonist.³⁹ Presumably, blockade of the

vasodilating effect normally produced by activity of β_2 receptors leaves unopposed α -adrenergic effects to provoke peripheral vasoconstriction with resulting hypertension.

Patients with peripheral vascular disease do not tolerate well the peripheral vasoconstriction associated with β_2 -receptor blockade. Indeed, the development of cold hands and feet is a common side effect produced by nonselective β -adrenergic antagonists in this population. Vasospasm associated with Raynaud disease is also accentuated by propranolol.

The principal antidysrhythmic effect of β -adrenergic blockade is to prevent the dysrhythmogenic effect of endogenous or exogenous catecholamines or sympathomimetics. This reflects a decrease in sympathetic nervous system activity. Membrane stabilization is probably of little importance in the antidysrhythmic effects produced by usual doses of β -adrenergic antagonists.

Treatment of Excess Myocardial Depression. The usual clinical manifestations of excessive myocardial depression produced by β -adrenergic blockade include bradycardia, hypotension, and cardiogenic shock.⁴⁰ Bronchospasm and depression of ventilation may also be associated with an overdose of β -adrenergic antagonist drugs. Seizures and prolonged intraventricular conduction of cardiac impulses are thought to be the result of local anesthetic properties of certain β -adrenergic antagonists (see [Table 19.1](#)). Hypoglycemia is a rare, but life-threatening, manifestation, of β -adrenergic antagonist overdose.

Excessive bradycardia and/or decreases in cardiac output due to drug-induced β -blockade should be treated initially with atropine in incremental doses of 7 $\mu\text{g}/\text{kg}$ IV. Atropine is likely to be effective by blocking vagal effects on the heart and thus unmasking any residual sympathetic nervous system innervation. If atropine is ineffective, drugs to produce direct positive chronotropic and inotropic effects are indicated. For example, continuous infusion of the nonselective β -adrenergic agonist isoproterenol, in doses sufficient to overcome competitive β -blockade, is appropriate. The necessary dose of isoproterenol may be 2 to 25 μg per minute IV (60 μg per minute IV was not effective in one report), which is 5 to 20 times the necessary dose in the absence of β -blockade.⁴⁰ When a pure β -adrenergic antagonist is responsible for excessive cardiovascular depression, a pure β_1 -adrenergic agonist such as dobutamine is recommended because isoproterenol, with β_1 - and β_2 -adrenergic agonist effects, could produce vasodilation before its inotropic effect develops. Dopamine and epinephrine are not recommended because α -adrenergic-induced vasoconstriction is likely to occur with the high doses required to overcome β -blockade.

Glucagon administered to adults, 1 to 10 mg IV followed by 5 mg per hour IV, has been used to effectively reverse the myocardial depression produced by β -adrenergic antagonists at normal doses because it does not exert its effects by means of β -adrenergic receptors. For example, glucagon stimulates adenylyl cyclase and increases intracellular cAMP concentrations independent of β -adrenergic receptors.⁴⁰ Calcium chloride, 250 to 1,000 mg IV, may also act independent of β -adrenergic receptors to offset excessive cardiovascular depression produced by β -adrenergic antagonists. Glucagon appears to be particularly effective in the presence of life-threatening bradycardia and has been described as the drug of choice to treat massive β -adrenergic antagonist overdose.⁴⁰

In the presence of life-threatening bradycardia that is unresponsive to pharmacologic therapy, it may be necessary to place a transvenous cardiac pacemaker, but without the caveat, that massive overdose may raise myocardial thresholds to prevent electromechanical capture. Hemodialysis should be reserved to remove minimally protein-bound, renally excreted β -adrenergic antagonists in patients refractory to pharmacologic therapy.

Airway Resistance

Nonselective β -adrenergic antagonists such as propranolol consistently increase airway resistance as a manifestation of bronchoconstriction due to blockade of β_2 receptors. These airway resistance effects are exaggerated in patients with preexisting obstructive airway disease. Because bronchodilation is a β_2 -adrenergic agonist response, selective β_1 -adrenergic antagonists such as bisoprolol, metoprolol, and esmolol are less likely than propranolol to increase airway resistance.

Metabolism

β -Adrenergic antagonists alter carbohydrate and fat metabolism. For example, nonselective β -adrenergic antagonists such as propranolol interfere with glycogenolysis that ordinarily occurs in response to release of epinephrine during hypoglycemia and emphasizes the need for β_2 -receptor activity in glycogenolysis.

Furthermore, the blunting of the tachycardiac response, an important warning sign of hypoglycemia in insulin-treated diabetics, is a distinct risk of β -adrenergic antagonists. For this reason, nonselective β -adrenergic antagonists are not recommended for administration to patients with diabetes mellitus being treated with insulin or oral hypoglycemics. Altered fat metabolism is evidenced by failure of sympathomimetics or sympathetic nervous system stimulation to increase plasma concentrations of free fatty acids in the presence of β -adrenergic blockade.

Distribution of Extracellular Potassium

Distribution of potassium across cell membranes is influenced by sympathetic nervous system activity as well as insulin. Specifically, stimulation of β_2 -adrenergic receptors seems to facilitate movement of potassium intracellularly. As a result, β -adrenergic blockade inhibits uptake of potassium into skeletal muscles, and the plasma concentration of potassium may be increased. Indeed, increases in the plasma concentration of potassium associated with infusion of this ion are greater in the presence of β -adrenergic blockade produced by propranolol (Figure 19.7).⁴¹ In animals, increases in the plasma concentration of potassium after administration of succinylcholine last longer when β -adrenergic blockade is present.⁴² However, this has not been conclusively demonstrated in patients.⁴³ In view of the speculated role of β_2 receptors in regulating plasma concentrations of potassium, it is likely that selective β_1 -adrenergic antagonists would impair skeletal muscle uptake of potassium less than nonselective β -adrenergic antagonists.

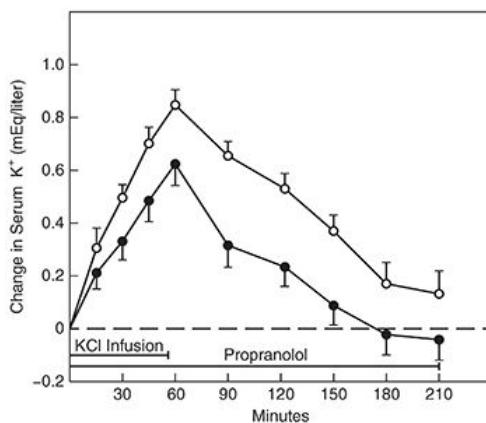


FIGURE 19.7 Increases in plasma (serum) potassium concentration (K^+) in response to infusion of potassium chloride (KCl) are greater in the presence of propranolol (clear circles) than in its absence (solid circles). (Mean \pm standard error.) From Rosa RM, Silva P, Young JB, et al. Adrenergic modulation of extrarenal potassium disposal. N Engl J Med. 1980;302(8):431-434. Copyright © 1980 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Interaction With Anesthetics

Myocardial depression produced by inhaled or injected anesthetics could be additive with depression produced by β -adrenergic antagonists. Nevertheless, clinical experience and controlled studies in patients and animals have confirmed that additive myocardial depression with β -adrenergic antagonists and anesthetics is not excessive, and thus, treatment with β -adrenergic antagonists may therefore be safely maintained throughout the perioperative period.¹ An exception may be patients treated with timolol in whom profound bradycardia has been observed in the presence of inhaled anesthetics.

Additive cardiovascular effects with inhaled anesthetics and β -adrenergic antagonists seem to be greatest with enflurane and least with isoflurane.¹ Sevoflurane and desflurane, like isoflurane, do not seem to be associated with significant additive cardiovascular effects when administered to patients being treated with β -adrenergic antagonists. Cardiac output and systemic blood pressure are similar with or without β -adrenergic blockade in the presence of one or two minimum alveolar concentrations of isoflurane.⁴⁴ Even acute hemorrhage does not alter the interaction between isoflurane and β -adrenergic antagonists.^{45,46} Cardiovascular responses to even high doses of opioids such as fentanyl are not altered by preexisting β -adrenergic blockade. In the presence of anesthetic drugs that increase sympathetic nervous system activity (ketamine), or when excessive sympathetic nervous system activity is present because of hypercarbia, the acute administration of a β -adrenergic antagonist may unmask direct negative inotropic effects of concomitantly administered anesthetics, with resulting decreases in systemic blood pressure and cardiac output.⁴⁷

Nervous System

β -Adrenergic antagonists may cross the blood–brain barrier to produce side effects. For example, fatigue and lethargy are commonly associated with chronic propranolol therapy. Vivid dreams are frequent, but psychotic reactions are rare. Memory loss and mental depression have been alleged to occur, although β -adrenergic antagonist therapy has not been shown to produce these effects.⁴⁸ A review of several clinical trials showed no significant increased risk of depressive symptoms and only small increased risks of fatigue and sexual dysfunction, although long-term and high dosage effects on the nervous system are less clear.^{49–51} Peripheral paresthesias have been described. Atenolol and nadolol are less lipid soluble than other β -adrenergic antagonists and thus may be associated with a lower incidence of CNS effects.

Fetus

β -adrenergic antagonists can cross the placenta and cause bradycardia, hypotension, and hypoglycemia, especially in lipophilic drugs like labetalol and propranolol but may be offset by high levels of protein binding reducing their effects on the fetus.^{52,53} Clinically, labetalol is listed by the US FDA as pregnancy category C and “potential benefits may outweigh the risks.” The American College of Obstetrician Gynecologists (ACOG) currently list PO and IV labetalol as first-line therapy for acute onset or emergent hypertension in pregnancy based on long term clinical use data. Per ACOG,⁵³ although breast is likely to contain beta antagonists, this is more pronounced in hydrophilic compounds with low protein binding such as atenolol and metoprolol and much less so in labetalol and propranolol. As such, ACOG continues to support the use of these medications in the breast feeding postparturient.

Withdrawal Hypersensitivity

Acute discontinuation of β -adrenergic antagonist therapy can result in excess sympathetic nervous system activity that manifests in 24 to 48 hours. Presumably, this enhanced activity reflects an increase in the number of β -adrenergic receptors (upregulation) that occurs during chronic antagonist therapy. Continuous infusion of propranolol, 3 mg per hour IV, is effective in maintaining therapeutic plasma concentrations in adult patients who cannot take drugs orally during the perioperative period.⁵⁴

Clinical Uses

Clinical uses of β -adrenergic antagonists are multiple and in equivalent doses, all β -adrenergic antagonists seem to be equally effective in producing desired therapeutic effects (**Table 19.3**). It is accepted that patients being treated with β -adrenergic receptor antagonists should have their medication continued uninterrupted through the perioperative period. It is also recommended that patients at high risk for myocardial ischemia and presenting for major surgery should be treated with β -adrenergic receptor antagonists beginning preoperatively and continuing into the postoperative period.

TABLE 19.3

Clinical uses of β -adrenergic blockers

Treatment of essential hypertension
Management of angina pectoris
Treatment of acute coronary syndrome
Perioperative β -adrenergic receptor blockade
Treatment of intraoperative myocardial ischemia
Suppression of cardiac dysrhythmias
Management of congestive heart failure
Prevention of excessive sympathetic nervous system activity
Preoperative preparation of hyperthyroid patients
Treatment of migraine headache

Treatment of Essential Hypertension

Chronic therapy with β -adrenergic antagonists results in gradual decreases in systemic blood pressure. The antihypertensive effect of β -adrenergic blockade is largely dependent on decreases in cardiac output due to decreased heart rate. Large doses of β -adrenergic antagonists may decrease myocardial contractility as well. In many patients, systemic vascular resistance remains unchanged. An important advantage in the use of β -adrenergic antagonists for the treatment of essential hypertension is the absence of orthostatic hypotension. Often, a β -adrenergic antagonist is used in combination with a vasodilator to minimize reflex baroreceptor-mediated increases in heart rate and cardiac output produced by the vasodilator. All orally administered β -adrenergic antagonists appear to be equally effective antihypertensive drugs. Release of renin from the juxtaglomerular apparatus that occurs in response to stimulation of β_2 receptors is prevented by nonselective β -adrenergic antagonists such as propranolol. This may account for a portion of the antihypertensive effect of propranolol, especially in patients with high circulating plasma concentrations of renin. With drug-induced decreases in secretion of renin and a decreased release of aldosterone, β -adrenergic antagonists will also prevent the compensatory sodium and water retention that accompanies treatment with a vasodilator.

Management of Angina Pectoris

Orally administered β -adrenergic antagonists are equally effective in decreasing the likelihood of myocardial ischemia manifesting as angina pectoris. This desirable response reflects drug-induced decreases in myocardial oxygen requirements secondary to decreased heart rate and myocardial contractility. The effective dose usually decreases resting heart rate to less than 60 beats per minute. A more important measure is the heart rate during exercise, which should not exceed 75% of the heart rate at which myocardial ischemia occurs.

The concept that β -adrenergic antagonists and calcium channel blockers act on different determinants of the myocardial oxygen supply-to-demand ratio suggests combined uses of these drugs would be beneficial in the management of patients with coronary artery disease. Nevertheless, the evidence from clinical studies suggests that patients managed with combined therapy do not experience greater beneficial therapeutic effects but may experience more adverse effects than if they had received optimal treatment with a single drug.⁵⁵

Treatment of Acute Coronary Syndrome

It used to be recommended that all patients who experience an acute myocardial infarction receive IV β -adrenergic antagonists as early as possible, whether or not they receive reperfusion therapy. Treatment with β -adrenergic antagonists is contraindicated in the presence of severe bradycardia, unstable left ventricular failure, and atrioventricular heart block. Relative contraindications to treatment with β -adrenergic antagonists include asthma or reactive airway disease, depression, excessive fatigue, and peripheral vascular disease. Diabetes mellitus is not a contraindication to treatment with β -adrenergic antagonists recognizing that signs of hypoglycemia may be masked.

A growing body of literature is rising against the use of β -blockers in patients who present with an acute coronary syndrome within the first 8 hours, especially if they present with ST elevation myocardial infarction

or cardiogenic shock.⁵⁶ The ST elevation myocardial infarction patients had a greater risk of developing cardiogenic shock after β -blocker administration, and those in shock had a greater risk of decompensating even further.⁵⁷ However, the incidence of nonfatal reinfarction and recurrent myocardial ischemia is decreased compared with patients in whom oral metoprolol was initiated 6 days following myocardial infarction.⁵⁸ β -Adrenergic antagonist prophylaxis after acute myocardial infarction is considered to be one of the most scientifically substantiated, cost-effective preventive medical treatments. Whether β -adrenergic antagonists can decrease mortality in patients with angina pectoris who have not yet experienced a myocardial infarction is unknown.

The cardioprotective effect of β -adrenergic antagonists is present with both cardioselective and nonselective drugs (see [Tables 19.1](#) and [19.2](#)). The mechanism of the cardioprotective effect is uncertain, but antidysrhythmic actions may be important. A nonselective β -adrenergic antagonist that prevents epinephrine-induced decreases in plasma potassium concentrations (a β_2 -mediated response) may be useful in decreasing the incidence of ventricular dysrhythmias.

Perioperative β -Adrenergic Receptor Blockade

Perioperative β -adrenergic receptor blockade is recommended for patients considered at risk for myocardial ischemia (known coronary artery disease, positive preoperative stress tests, diabetes mellitus treated with insulin, left ventricular hypertrophy) during high-risk surgery (vascular surgery, thoracic surgery, intraperitoneal surgery, anticipated large blood loss).^{59,60} The goal of preoperative therapy is a resting heart rate between 65 and 80 beats per minute.⁶¹ All β -adrenergic receptor antagonists except those with intrinsic sympathetic nervous system activity decrease mortality. Perioperative myocardial ischemia is the single most important potentially reversible risk factor for mortality and cardiovascular complications after noncardiac surgery. Administration of atenolol for 7 days before and after noncardiac surgery in patients at risk for coronary artery disease may decrease mortality and the incidence of cardiovascular complications for as long as 2 years after surgery.¹⁵ In another report, administration of atenolol IV before induction of anesthesia and every 12 hours after noncardiac surgery for 7 days to patients at high risk for coronary artery disease reduced the incidence of postoperative myocardial ischemia by 30% to 50%.¹⁶ Decreases in perioperative myocardial ischemia are associated with reductions in the risk for death at 24 months. The incidence of bronchospasm, hypotension, bradycardia, and cardiac dysrhythmias was not increased in treated patients. The mechanism for the beneficial effects of perioperative β -adrenergic receptor blockade is not known but is most likely multifactorial ([Table 19.4](#)). It is not known if patients with cardiac risk factors but no signs of underlying coronary artery disease will benefit from perioperative administration of a β -adrenergic antagonist.⁶²

TABLE 19.4

Possible explanations for cardioprotective effects produced by perioperative β -adrenergic receptor blockade

Decreased myocardial oxygen consumption and demand
Less stress on potentially ischemic myocardium owing to decreased heart rate and myocardial contractility
Attenuation of effects of endogenous catecholamines
Redistribution of coronary blood flow to ischemic areas
Increased coronary blood flow owing to increased diastolic time
Plaque stabilization owing to decrease in shear forces
Cardiac antidysrhythmic effects
Antiinflammatory effects

Preoperatively, oral therapy can be initiated with atenolol 50 mg or bisoprolol 5 to 10 mg daily or metoprolol 25 to 50 mg twice daily. If the patient is seen the morning of surgery, atenolol 5 to 10 mg IV or metoprolol 5 to 10 mg IV can be titrated. Esmolol is an acceptable drug to achieve β -adrenergic receptor blockade during surgery and postoperatively in the intensive care unit where continuous IV infusions can be

monitored. Alternatively, IV atenolol or metoprolol can be administered until the patient can take oral atenolol, metoprolol, or bisoprolol. β -Adrenergic receptor antagonists with sympathomimetic actions are not likely selections to produce perioperative β -blockade. The Perioperative Ischemic Evaluation trial has raised concerns over regimens that start β -blockers in the acute preoperative setting due to an all-cause increased mortality that is driven by an increase in cerebrovascular events. Criticisms of the Perioperative Ischemic Evaluation trial⁶³ point to its very aggressive escalation regimen (as much as 400 mg metoprolol succinate dosed in 24 hours) without regard to patient's baseline hemodynamics (systolic and mean pressure reductions of >30% below preoperative levels), which is well known to cause cerebrovascular hypoperfusion and infarction. This has prompted many practitioners to only start low-dose β -blocker regimens in the preoperative period or to hold initiation until postoperatively.

Treatment of Intraoperative Myocardial Ischemia

Appearance of evidence of myocardial ischemia on the electrocardiogram or as wall motion abnormalities on the transesophageal echocardiogram may benefit from treatment with a β -adrenergic receptor blocking drug, assuming the absence of contraindications (severe reactive airway disease, right ventricular ischemia, bradycardia, shock, or left ventricular failure) and the presence of an adequate concentration of inhaled anesthetic drugs. The drug selected should be titrated to the desired heart rate (about 60 beats per minute) to attenuate myocardial ischemia. Treatment options include esmolol (1-1.5 mg/kg IV followed by a continuous infusion of 50-300 μ g/kg per minute), metoprolol (5 mg IV), atenolol (5-10 mg IV), or propranolol (1-10 mg IV). The advantage of esmolol is the ability to titrate its effects to the desired heart rate. Nitroglycerin is often added to this treatment regimen.

Suppression of Cardiac Dysrhythmias

β -Adrenergic receptor blocking drugs are effective in the treatment of cardiac dysrhythmias as a result of enhanced sympathetic nervous system stimulation (thyrotoxicosis, pheochromocytoma, perioperative stress). Intravenous esmolol and propranolol are effective for controlling the ventricular response rate to atrial fibrillation and atrial flutter. These drugs are also effective for controlling atrial dysrhythmias following cardiac surgery. Propranolol may be effective for controlling torsades de pointes in patients with prolonged QTc intervals on the electrocardiogram. Acebutolol, metoprolol, atenolol, propranolol, and timolol are approved for prevention of sudden death following acute myocardial infarction.

Management of Congestive Heart Failure

Controlled studies have demonstrated that metoprolol, carvedilol, and bisoprolol improve ejection fraction and increase survival in patients in chronic heart failure (see [Table 19.2](#)). Sustained-release metoprolol is associated with improved survival.⁶⁴ Carvedilol, a nonselective β -blocker with vasodilator and antioxidant properties, has been shown to decrease mortality associated with congestive heart failure.⁶⁵ When β -blocking drugs are used to treat congestive heart failure, the initial doses of β -blockers should be minimal and gradually increased.

Prevention of Excessive Sympathetic Nervous System Activity

β -Adrenergic blockade is associated with attenuated heart rate and blood pressure changes in response to direct laryngoscopy and tracheal intubation.^{1,66} Hypertrophic obstructive cardiomyopathies are often treated with β -adrenergic antagonists. Tachycardia and cardiac dysrhythmias associated with pheochromocytoma and hyperthyroidism are effectively suppressed by propranolol. The likelihood of cyanotic episodes in patients with tetralogy of Fallot is minimized by β -blockade. Propranolol has been used intraoperatively to prevent reflex baroreceptor-mediated increases in heart rate evoked by vasodilators administered to produce controlled hypotension. Even anxiety states as caused by public speaking have been treated with propranolol.

Preoperative Preparation of Hyperthyroid Patients

Thyrotoxic patients can be prepared for surgery in an emergency by IV administration of propranolol or esmolol or electively by oral administration of propranolol (40-320 mg daily).^{67,68} Advantages of β -

adrenergic antagonists include rapid suppression of excessive sympathetic nervous system activity and elimination of the need to administer iodine or antithyroid drugs.

Combined α - and β -Adrenergic Receptor Antagonists

Labetalol

Labetalol is a parenteral and oral antihypertensive drug that exhibits selective α_1 - and nonselective β_1 - and β_2 -adrenergic antagonist effects (**Figure 19.8**).^{69,70} Presynaptic α_2 receptors are spared by labetalol such that released norepinephrine can continue to inhibit further release of catecholamines via the negative feedback mechanism resulting from stimulation of α_2 receptors. Labetalol is one-fifth to one-tenth as potent as phentolamine in its ability to block α receptors and is approximately one-fourth to one-third as potent as propranolol in blocking β receptors. In humans, the β to α blocking potency ratio is 3:1 for oral labetalol and 7:1 for IV labetalol.

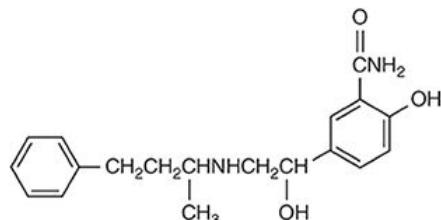


FIGURE 19.8 Labetalol.

Pharmacokinetics

Metabolism of labetalol is by conjugation of glucuronic acid with 5% of the drug recovered unchanged in urine. The elimination half-time is 5 to 8 hours and is prolonged in the presence of liver disease and unchanged by renal dysfunction.

Cardiovascular Effects

Administration of labetalol lowers systemic blood pressure by decreasing systemic vascular resistance (α_1 -blockade), whereas reflex tachycardia triggered by vasodilation is attenuated by simultaneous β -blockade. Cardiac output remains unchanged. In addition to producing vasodilation by α_1 -blockade, labetalol may cause vasodilation that is mediated by β_2 -adrenergic agonist activity.⁷¹ The maximum systemic blood pressure-lowering effect of an IV dose of labetalol (0.1-0.5 mg/kg) is present in 5 to 10 minutes.

Clinical Uses

Labetalol is a safe and effective treatment for hypertensive emergencies. For example, labetalol has been administered IV to control severe hypertension that may be associated with an epinephrine overdose as may occur during submucosal injection to produce surgical hemostasis.⁷² Conversely, caution has been urged in using β -adrenergic blockers to treat phenylephrine and epinephrine overdose resulting from systemic absorption following topical application.²⁶ Large bolus doses of labetalol (2 mg/kg IV) administered to treat hypertensive emergencies may result in excessive decreases in blood pressure, whereas smaller doses (20-80 mg IV) are less likely to produce undesirable decreases in blood pressure.^{73,74} Repeated doses of labetalol, 20 to 80 mg IV, may be administered about every 10 minutes until the desired therapeutic response is achieved.⁷⁴ Rebound hypertension after withdrawal of clonidine therapy and hypertensive responses in patients with pheochromocytoma can be effectively treated with labetalol. Labetalol is also effective in the treatment of angina pectoris. Availability of both an oral (100-600 mg twice a day) and IV preparation is useful for converting a patient with a hypertensive crisis to oral therapy after initial control with IV therapy.

Labetalol, 0.1 to 0.5 mg/kg IV, can be administered to anesthetized patients to attenuate increases in heart rate and blood pressure that are presumed to result from abrupt increases in the level of surgical

stimulation. It is possible that existing depressant effects of the anesthetic drugs could accentuate the blood pressure-lowering properties of labetalol. In contrast to the results with nitroprusside, controlled hypotension produced with intermittent injections of labetalol, 10 mg IV, is not associated with increases in heart rate, intrapulmonary shunt, or cardiac output.⁷⁵

Side Effects

Orthostatic hypotension is the most common side effect of labetalol therapy. Bronchospasm is possible in susceptible patients, reflecting the β -adrenergic antagonist effects of labetalol. Other adverse effects associated with β -adrenergic antagonists (congestive heart failure, bradycardia, heart block) are a potential risk of labetalol therapy, but the likely incidence and severity is substantially decreased. Incomplete α -adrenergic blockade in the presence of more complete β -blockade could result in excessive α stimulation.⁷² Fluid retention in patients treated chronically with labetalol is the reason for combining this drug with a diuretic during prolonged therapy.

Carvedilol

Carvedilol is a nonselective β -adrenergic receptor antagonist with α_1 -blocking activity. This drug has no intrinsic β -adrenergic agonist effect. Following oral administration, carvedilol is extensively metabolized to products with pharmacologic activity possessing weak vasodilator actions. The elimination half-time is 7 to 10 hours, and protein binding is extensive. Carvedilol is indicated for the treatment of mild to moderate congestive heart failure owing to ischemia or cardiomyopathy (see [Table 19.2](#)). This drug is also useful for the treatment of essential hypertension.

Calcium Channel Blockers

Calcium channel blockers (also known as **calcium entry blockers** and **calcium antagonists**) are a diverse group of structurally unrelated compounds that selectively interfere with inward calcium ion movement across myocardial and vascular smooth muscle cells.^{76,77} Calcium ions play a key role in the electrical excitation of cardiac cells and vascular smooth muscle cells.

Commercially available calcium channel blockers are classified based on chemical structure as phenylalkylamines, dihydropyridines, and benzothiazepines ([Table 19.5](#) and [Figure 19.9](#)). The phenylalkylamines and benzothiazepines are selective for the atrioventricular node, whereas the dihydropyridines are selective for the arteriolar beds.⁷⁸ Common side effects of calcium channel blockers include systemic hypotension, peripheral edema, flushing, and headache. The various calcium channel blockers differ in terms of side effects, usual doses, metabolism, and duration of action ([Tables 19.6](#) and [19.7](#)). Despite sharing the commonality of calcium channel inactivation, the classes of calcium channel blockers have different molecular mechanisms of action at the calcium channel subtypes, different tissue specificity, and different physiologic responses.⁷⁹

TABLE 19.5	
Classification of calcium channel blockers	
Phenylalkylamine	
Verapamil	
Dihydropyridines	
Clevidipine	
Nifedipine	
Nicardipine	
Nimodipine	
Isradipine	
Felodipine	
Amlodipine	

Benzothiazepine

Diltiazem

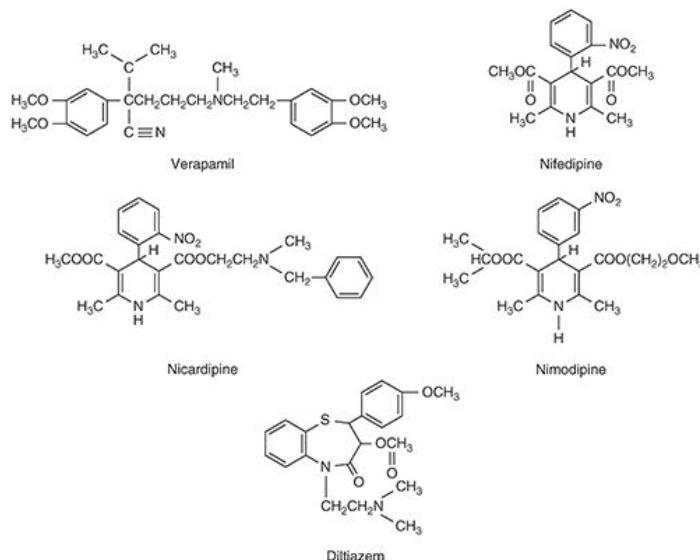


FIGURE 19.9 Calcium channel blockers.

TABLE 19.6

Comparative pharmacologic effects of calcium channel blockers

	Verapamil	Nifedipine	Nicardipine	Diltiazem
Systemic blood pressure	Decrease	Decrease	Decrease	Decrease
Heart rates	Decrease	Increase to no change	Increase to no change	Decrease
Myocardial depression	Moderate	Moderate	Slight	Moderate
Sinoatrial node depression	Moderate	None	None	Slight
Atrioventricular node conduction	Marked	None	None	Moderate depression
Coronary artery dilation	Moderate	Marked	Greatest	Moderate
Peripheral artery dilation	Moderate	Marked	Marked	Moderate

TABLE 19.7

Pharmacokinetics of calcium channel blockers*

	Verapamil	Nifedipine	Nicardipine	Nimodipine	Diltiazem
Dosage					
Oral	80-160 mg every 8 hours	10-30 mg every 8 hours	20 mg every 8 hours	30-60 mg every 4-6 hours	60-90 mg every 8 hours
Intravenous	75-150 µg/kg	5-15 µg/kg	2-5 mg/h	10 µg/kg	75-150 µg/kg
Absorption (%)					
Oral	>90	>90	99	>90	>90
Bioavailability	10-20	65-70	30	5-10	40
Onset of effect (minutes)					

Oral	<30	<20	20-60	30-90	30
Sublingual		3			
Intravenous	1-3	1-3	1-3	1-3	1-3
First-pass hepatic extraction after oral administration (%)	75-90	40-60	20-40	90	70-80
Protein binding (%)	83-93	92-98	95	99	98
Clearance					
Renal (%)	70	80	55	20	35
Hepatic (%)	15	<15	45	80	60
Active metabolites	Yes	No	No	Yes	Yes
Therapeutic plasma concentration (ng/mL)	50-50	10-100	5-100	10-30	100-250
Elimination half-time (hours)	3-7	3-7	3-5	2	4-6

*Adapted by permission from Springer: Durand PG, Lehot JJ, Foëx P. Calcium-channel blockers and anaesthesia. *Can J Anaesth.* 1991;38(1):75-89. Copyright © 1991 Springer Nature; Reprinted with permission from Reves JG, Kissin I, Lell WA, et al. Calcium entry blockers: uses and implications for anesthesiologists. *Anesthesiology.* 1982;57(6):504-518. Copyright © 1982 American Society of Anesthesiologists, Inc.

Mechanism of Action

Calcium channel blockers bind to receptors on voltage-gated calcium ion channels (L, long-lasting; N, neural; and T, transient opening subtypes) resulting in maintenance of these channels in an inactive (closed) state. As a result, calcium influx is decreased, and there is a reduction in intracellular calcium. The L-type channel (slow channel) has five subunits: α_1 , α_2 , β , γ , and δ . The α_1 subunit forms the central part of the channel and provides the main pathway for calcium ion entry into cells. All clinically used calcium channel blockers bind to a unique site on the α_1 subunit of the L-type calcium channels and thus diminish entry of calcium ions into cells. These structurally diverse drugs differ in their tissue selectivity, their binding site location on the α_1 subunit, and their mechanism of calcium blockade.

Voltage-gated calcium ion channels are present in the cell membranes of skeletal muscle, vascular smooth muscle, cardiac muscle, mesenteric muscle, glandular cells, and neurons ([Figure 19.10](#)).⁷⁸ Calcium ion influx through L-type calcium channels is responsible for phase 2 of the cardiac action potential, which is important in excitation/contraction coupling in cardiac and vascular smooth muscle and depolarization in sinoatrial and atrioventricular nodal tissue. Thus, blockade of slow calcium channels by calcium channel blockers predictably results in slowing of the heart rate, reduction in myocardial contractility, decreased speed of conduction of cardiac impulses through the atrioventricular node, and vascular smooth muscle relaxation.⁸⁰

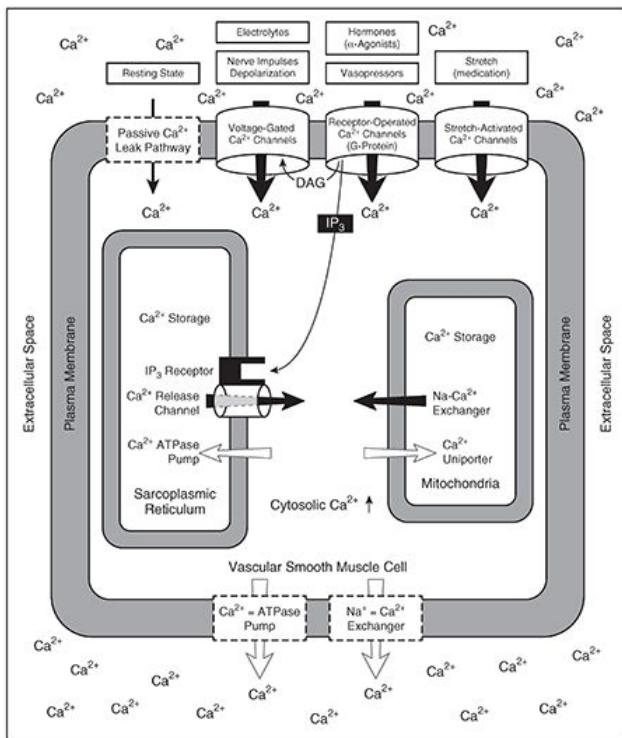


FIGURE 19.10 Calcium ion entry and exit from a vascular smooth muscle cell. Calcium enters the cytosol (black arrows) of the vascular smooth muscle cell either from the extracellular space through the plasma membrane (top of diagram) or from the intracellular storage areas. The primary entry sites for calcium ions are the voltage-gated channels. *Reprinted with permission from Kanneganti M, Halpern NA. Acute hypertension and calcium-channel blockers. New Horiz. 1996;4(1):19-25.*

Direct activation of the vascular smooth muscle cell voltage-gated channels by neural impulses initiates an action potential, calcium ion influx, and myofilament contraction (see [Figure 19.10](#)).⁷⁸ This process is known as **excitation-contraction coupling**. The intracellular calcium combines with calmodulin, the calcium-binding protein, to form the calcium-calmodulin complex. This complex activates myosin and causes the formation of cross-bridges with actin. These cross-bridges begin the process of muscular contraction.

Pharmacologic Effects

The pharmacologic effects of calcium channel blockers may be predicted by considering the normal role of calcium ions in the production of action potentials, especially in cardiac cells. It is predictable that calcium channel blockers will produce decreased myocardial contractility, decreased heart rate, decreased activity of the sinoatrial node, decreased rate of conduction of cardiac impulses through the atrioventricular node, and vascular smooth muscle relaxation with associated vasodilation and decreases in systemic blood pressure.^{80,81} Calcium channel blockers produce these effects to varying degrees (see [Table 19.6](#)).

All of the calcium channel blockers are effective for the treatment of coronary artery spasm. Calcium channel blockers decrease vascular smooth muscle contractility, thereby increasing coronary blood flow and causing peripheral vasodilation with reductions in systemic vascular resistance and systemic blood pressure. These drug-induced responses contribute to the anti-ischemic effects characteristic of calcium channel blockers. As calcium channel blockers dilate the coronary arteries via a mechanism that is different from that of nitrates, the two classes of drugs complement each other in the treatment of coronary artery spasm. Calcium channel blockers are also effective for the treatment of chronic stable angina pectoris caused by fixed obstructive coronary artery lesions and for the treatment of unstable angina pectoris.

All calcium channel blockers exert negative inotropic effects, which are most significant with verapamil and diltiazem.

Phenylalkylamines

The phenylalkylamines bind to the intracellular portion of the L-type channel α_1 subunit when the channel is in an open state and conceptually occlude the channel ([Figure 19.11](#)).⁷⁸

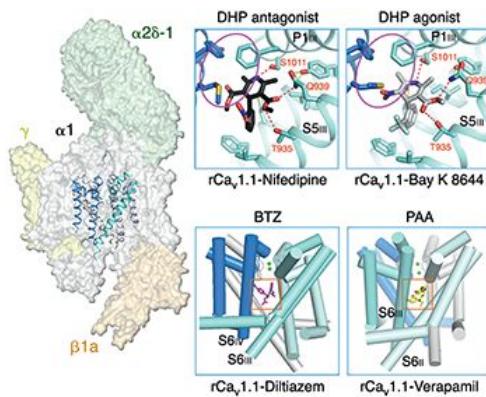


FIGURE 19.11 A view on how both agonists and antagonists interact with a voltage-gated calcium channel opens up avenues for understanding channel gating and new ligand design. Abbreviations: BTZ, benzothiazepines; DHP, 1,4-dihydropyridines; PAA, phenylalkylamines; rCA, recombinant Ca proteins. *Reprinted with permission from Zhao Y, Huang G, Wu J, et al. Molecular basis for ligand modulation of a mammalian voltage-gated Ca2+ channel. Cell. 2019;177(6):1495-1506.e12. Copyright © 2019 Elsevier. With permission.*

Verapamil

Verapamil is a synthetic derivative of papaverine that is supplied as a racemic mixture. The dextroisomer of verapamil is devoid of activity at slow calcium channels and instead acts on fast sodium channels, accounting for the local anesthetic effects of verapamil (1.6 times as potent as procaine).⁸² The levoisomer of verapamil is specific for slow calcium channels, and the predominance of this action accounts for the classification of verapamil as a calcium-blocking drug.

Side Effects

Verapamil has a major depressant effect on the atrioventricular node, a negative chronotropic effect on the sinoatrial node, a negative inotropic effect on cardiac muscle, and a moderate vasodilating effect on coronary and systemic arteries. The negative inotropic effects of verapamil seem to be exaggerated in patients with preexisting left ventricular dysfunction. For these reasons, verapamil should not be administered to patients in heart failure or patients with severe bradycardia, sinus node dysfunction, or atrioventricular nodal block. Likewise, this drug's negative inotropic and chronotropic effects may be enhanced in the presence of concomitant treatment with β -adrenergic antagonists. Isoproterenol may be useful to increase heart rate in the presence of drug-induced heart block. Verapamil may precipitate ventricular dysrhythmias in patients with Wolff-Parkinson-White syndrome.

Clinical Uses

Verapamil is effective in the treatment of supraventricular tachydysrhythmias, reflecting its primary site of action on the atrioventricular node (see [Chapter 21](#)). The mild vasodilating effects produced by verapamil make this drug useful in the treatment of vasospastic angina pectoris and essential hypertension. Indeed, calcium channel blockers are as effective as β -blockers in relieving angina pectoris. Verapamil is not as active as nifedipine in its effects on vascular smooth muscle and therefore causes a less pronounced decrease in systemic blood pressure and less reflex peripheral sympathetic nervous system activity. Verapamil is effective in the treatment of symptomatic hypertrophic cardiomyopathy with or without left ventricular outflow

obstruction.⁸³ Calcium channel antagonists should not be routinely administered for acute myocardial infarction as postinfarction mortality is not decreased.⁸⁴

Pharmacokinetics

Oral verapamil is almost completely absorbed, but extensive hepatic first-pass metabolism limits bioavailability to 10% to 20% (see [Table 19.7](#)). As a result, the oral dose (80–160 mg 3 times daily) is about 10 times the IV dose. The therapeutic plasma concentration of verapamil is 100 to 300 ng/mL. The activity of oral verapamil peaks in 30 to 45 minutes compared with about 15 minutes following IV administration. Pharmacologic effects following IV administration of verapamil appear within 2 to 3 minutes and may last 6 hours.

Demethylated metabolites of verapamil predominate, with norverapamil possessing sufficient activity to contribute to the antidyshhythmic properties of the parent drug. In view of the nearly complete hepatic metabolism of verapamil, almost none of the drug appears unchanged in the urine. Conversely, an estimated 70% of an injected dose of verapamil is recovered in urine as metabolites, and about 15% is excreted via bile. Chronic oral administration of verapamil or the presence of renal dysfunction leads to the accumulation of norverapamil.

The elimination half-time of verapamil is 6 to 12 hours, and this may be prolonged in patients with liver disease. In this regard, chronic treatment with verapamil has rarely been associated with increased plasma concentrations of transaminase enzymes. Like nifedipine, verapamil is highly protein bound (90%), and the presence of other drugs (lidocaine, diazepam, propranolol) can increase the pharmacologically active, unbound portion of the drug.

Dihydropyridines

The dihydropyridines prevent calcium entry into the vascular smooth cells by extracellular allosteric modulation of the L-type voltage-gated calcium ion channels (see [Figure 19.11](#)).⁷⁸ The primary affinity of the dihydropyridines clevidipine, nifedipine, nicardipine, isradipine, felodipine, and amlodipine is for the peripheral arterioles, whereas nimodipine favors cerebral vessels. The vasodilating effects of these drugs on venous capacitance vessels are minimal. As with other peripheral vasodilators, a reflex tachycardia attributed to sympathetic nervous system activity or baroreceptor reflexes may be observed with the acute administration of dihydropyridines.

Nifedipine

Nifedipine is a dihydropyridine derivative with greater coronary and peripheral arterial vasodilator properties than verapamil. There is minimal effect on venous capacitance vessels. Unlike verapamil, nifedipine has little or no direct depressant effect on sinoatrial or atrioventricular node activity. Peripheral vasodilation and the resulting decrease in systemic blood pressure produced by nifedipine activate baroreceptors, leading to increased peripheral sympathetic nervous system activity most often manifesting as an increased heart rate. This increased sympathetic nervous system activity counters the direct negative inotropic, chronotropic, and dromotropic effects of nifedipine. Nevertheless, nifedipine may produce excessive myocardial depression, especially in patients with preexisting left ventricular dysfunction or concomitant therapy with a β -adrenergic antagonist drug. The presence of aortic stenosis may also exaggerate the cardiac depressant effects of nifedipine.

Clinical Uses

Nifedipine is administered orally with a 10- to 30-mg dose, producing an effect in about 20 minutes with a peak effect between 60 and 90 minutes. Nifedipine is used to treat patients with angina pectoris, especially that due to coronary artery vasospasm.

Pharmacokinetics

Absorption of an oral or sublingual dose of nifedipine is about 90%, with onset of an effect being detectable within about 20 minutes after administration (see [Table 19.7](#)). It is likely that most of the absorption of

sublingual nifedipine is via the gastrointestinal tract from swallowed saliva. Protein binding approaches 90%. Hepatic metabolism is nearly complete, with elimination of inactive metabolites principally in urine (about 80%) and, to a lesser extent, in bile. The elimination half-time is 3 to 7 hours.

Side Effects

The side effects of nifedipine include flushing, vertigo, and headache. Less common side effects include peripheral edema (venous congestion), hypotension, paresthesias, and skeletal muscle weakness. Glucose intolerance and hepatic dysfunction occur rarely, but nifedipine has been associated with both an increase in glomerular filtration rate and renal blood flow at low doses or may induce renal dysfunction if perfusion pressure is dropped enough to cause a loss of blood flow resulting in a prerenal injury pattern. Abrupt discontinuation of nifedipine has been associated with coronary artery vasospasm.

Nicardipine

Nicardipine lacks effects on the sinoatrial node and atrioventricular node and has minimal myocardial depressant effects. This drug has the greatest vasodilating effects of all the calcium entry blockers, with vasodilation being particularly prominent in the coronary arteries. Combination with a β -adrenergic antagonist for the treatment of angina is a consideration because dihydropyridine calcium channel blockers do not significantly depress the sinoatrial node. Of all the antianginal drugs, the dihydropyridine calcium channel blockers produce the greatest dilatation of the peripheral arterioles. Therefore, either nifedipine or nicardipine may be particularly useful in patients who have residual hypertension despite β -adrenergic blockade.

Nicardipine is available in IV and oral preparations (other dihydropyridine calcium channel blockers are available only as oral preparations) and is highly lipophilic with a nearly complete gastrointestinal absorption but a very high first-pass metabolism reducing its bioavailability to only about 35%. The IV formulation follows a triexponential decline in plasma concentrations with an α half-life of 2.7 minutes, a β half-life of 44.8 minutes, and a terminal γ half-life of 14.4 hours. Therefore, with short-term infusions, its functional vasodilation only lasts 9 to 15 minutes, but it is this long elimination half-time is the basis for the recommendation that about 72 hours should elapse before increasing the oral doses. Nicardipine is metabolized in the liver and is highly protein bound (about 95%). The side effects of nicardipine are similar to nifedipine.

Clinical Uses

Although no longer recommended, nicardipine has been used as a tocolytic drug having a similar tocolytic effect as salbutamol but with fewer side effects.⁸⁵ When nicardipine is administered as a tocolytic, it binds to the inside of myometrial L-type voltage-dependent calcium ion channels, causing them to remain closed, and thus inhibits uterine contractility. Pulmonary edema associated with salbutamol used as a tocolytic has also been reported in a parturient treated with nicardipine.⁸⁶ Nicardipine, 40 μ g/kg IV administered immediately before performing electroconvulsive therapy, is effective in blunting acute hemodynamic responses to the treatment.⁸⁷

Clevidipine

Clevidipine is a third-generation dihydropyridine that is extremely lipophilic and ultrashort acting. It is U.S. Food and Drug Administration approved for the treatment of acute, severe hypertension and is only available in an IV form. It is cleared by plasma esterases with a metabolism half-life of approximately 1 minute that is unaffected by either liver or kidney dysfunction. However, in patients with pseudocholinesterase deficiency, metabolism was significantly delayed and functional half-life times were increased by approximately 32%.

Dosing is a simple protocol that starts at 1 to 2 mg per hour and is doubled every 90 seconds until blood pressure approaches goal, and then increases are reduced to 1 to 2 mg per hour again and only increased every 5 to 10 minutes. Although median dosing range is 4 to 8 mg per hour, doses as high as 32 mg per hour have been used but not studied extensively. The preparation of clevidipine comes as a 0.2-g of lipid per milliliter and necessitates adjustments to both enteral and parenteral nutrition at higher doses. Common side

effects include hypotension as well as tachycardia, and it bears a warning against use in hyperlipidemic states, acute or chronic pancreatitis, and heart failure with reduced ejection fraction as higher dose infusions have been associated with a negative inotropic effect that could precipitate acute decompensation.

Nimodipine

Nimodipine is a highly lipid-soluble analogue of nifedipine. Lipid solubility facilitates its entrance into the CNS, where it blocks the influx of extracellular calcium ions necessary for contraction of large cerebral arteries.

Clinical Uses

The lipid solubility of nimodipine and its ability to cross the blood–brain barrier is responsible for the potential value of this drug in treating patients with subarachnoid hemorrhage.

Cerebral Vasospasm

The vasodilating effect of nimodipine on cerebral arteries is uniquely valuable in preventing or attenuating cerebral vasospasm that often accompanies subarachnoid hemorrhage.⁸⁸ The initial event in the development of vasospasm may be an intracellular influx of calcium ions that cause contraction of smooth muscle cells in large cerebral arteries. Administration of nimodipine, 0.7 mg/kg orally as an initial dose followed by 0.35 mg/kg every 4 hours for 21 days, is associated with a decreased incidence of neurologic deficits due to cerebral vasospasm in patients who had experienced subarachnoid hemorrhage.⁸⁹ Blood and cerebrospinal fluid levels of nimodipine with this dosing regimen were 6.9 and 0.77 ng/mL, respectively. In comatose patients who cannot take oral medications, the recommendation is to extract the contents of the nimodipine capsule into a syringe and administer the drug into a nasogastric tube. To ensure delivery of the drug into the stomach via a nasogastric tube, it is necessary to add up to 30 mL of saline to the nimodipine-containing solution.⁹⁰ Side effects have not been observed with the oral administration of nimodipine. Symptoms of excessive nimodipine effect would be expected to be related to cardiovascular effects such as peripheral vasodilation with associated systemic hypotension. Theoretically, drug-induced cerebral vasodilation could evoke increases in intracranial pressure, particularly in patients with preexisting decreases in intracranial compliance.

Cerebral Protection

Nimodipine has also been evaluated for cerebral protection after global ischemia as associated with cardiac arrest. The theoretical basis for considering calcium channel blockers for this purpose is the observation that lack of oxygen interferes with maintenance of the normal calcium ion gradient across cell membranes, leading to a massive increase (at least 200-fold) in the intraneuronal concentrations of this ion. In this regard, nimodipine is associated with improved neurologic outcome when used for subarachnoid hemorrhage after aneurysm rupture.^{91,92} The dose of nimodipine used (10 µg/kg IV followed by 1 µg/kg per minute IV) was associated with decreases in blood pressure that responded to infusion of fluids and/or dopamine.

Amlodipine

Amlodipine is a dihydropyridine derivative that is available for only oral administration (5-10 mg) resulting in a peak plasma concentration in 6 to 12 hours. Elimination half-time is 30 to 40 hours, and about 90% of the drug undergoes hepatic metabolism to inactive products. Amlodipine appears to have minimal detrimental effects on myocardial contractility and provides anti-ischemic effects comparable to β-blockers in patients with acute coronary syndrome.⁸⁴ The combination of amlodipine and β-blockers may be more effective in the treatment of myocardial ischemia than either drug alone.

Benzothiazepines

Benzothiazepines act at the L-type channel passing directly through the poor and blocking calcium entry like verapamil (see [Figure 19.11](#)).⁹³ The benzothiazepine diltiazem may have two additional effects: It may act on

the sodium-potassium pump, decreasing the amount of intracellular sodium available for exchange with extracellular calcium, and it may inhibit calcium-calmodulin binding.

Diltiazem

Diltiazem, like verapamil, blocks predominantly the calcium channels of the atrioventricular node and is therefore a first-line medication for the treatment of supraventricular tachydysrhythmias (see [Chapter 21](#)). It may also be used for the chronic control of essential hypertension. The effects of diltiazem on the sinoatrial and atrioventricular nodes and its vasodilating properties appear to be intermediate between those of verapamil and the dihydropyridines. Diltiazem exerts minimal cardiodepressant effects and is unlikely to interact with β -adrenergic blocking drugs to decrease myocardial contractility.⁵⁵

Clinical Uses

The clinical use and drug interactions for diltiazem are similar to those of verapamil. Diltiazem is available as an oral capsule and can also be administered IV, especially for the management of angina pectoris. The recommended IV dose is 0.25 to 0.35 mg/kg over 2 minutes and is repeated in 15 minutes, if needed. After the initial IV dose, diltiazem can be given by continuous infusion of about 10 mg per hour for up to 24 hours.

Pharmacokinetics

Oral absorption of diltiazem is excellent with an onset of action in 15 minutes and a peak effect in about 30 minutes (see [Table 19.7](#)). The drug is 70% to 80% bound to proteins and is excreted as inactive metabolites principally in bile (about 60%) and, to a lesser extent, in urine (about 35%). Active metabolites of diltiazem include desacetyl diltiazem and desmethyl diltiazem. The elimination half-time for the parent drug is 4 to 6 hours and about 20 hours for its metabolites. As with verapamil, liver disease may necessitate a decrease in the dosage of diltiazem.

Drug Interactions

The known pharmacologic effects of calcium channel blockers on cardiac, skeletal, and vascular smooth muscle, as well as on the conduction velocity of cardiac impulses, make drug interactions possible.⁷⁷ Verapamil and diltiazem have depressant effects on the generation of cardiac action potentials at the sinoatrial node and slow the movement of cardiac impulses through the atrioventricular node. Therefore, patients with preexisting cardiac conduction abnormalities may experience greater degrees of atrioventricular heart block with concurrent administration of β -blockers or digoxin. Myocardial depression and peripheral vasodilation produced by volatile anesthetics could be exaggerated by similar actions of calcium channel blockers. The vasodilatory effects of calcium channel blockers could result in exaggerated systemic hypotension should these drugs be administered to hypovolemic patients.

The likelihood of adverse circulatory changes due to interactions between calcium channel blockers and anesthetic drugs would seem to be greater in patients with preexisting atrioventricular heart block or left ventricular dysfunction. Nevertheless, treatment with calcium channel blockers can be continued until the time of surgery without risk of significant drug interactions, especially with respect to conduction of cardiac impulses.⁹⁴ Toxicity reflecting an overdose of calcium channel blockers may be partially reversed with IV administration of calcium or dopamine.

Anesthetic Drugs

Calcium channel blockers as a class are vasodilators and myocardial depressants. In fact, the negative inotropic effects, depressant effects on sinoatrial node function, and peripheral vasodilating effects of these drugs and those of volatile anesthetics are similar, and there is evidence that volatile anesthetics inhibit calcium channels independent of protein kinase C.^{95,96} For these reasons, calcium channel blockers must be administered with caution to patients with impaired left ventricular function or hypovolemia. Patients treated with a combination of β -adrenergic blockers and nifedipine tolerate high-dose fentanyl anesthesia and do not show evidence of additive depression of cardiac function when verapamil is infused.⁹⁷ Conversely, in anesthetized patients with preexisting left ventricular dysfunction, administration of verapamil is associated

with myocardial depression and decreased cardiac output.⁹⁸ Furthermore, IV administration of verapamil or diltiazem during open chest surgery in patients with depressed ventricular function and anesthetized with a volatile anesthetic may be associated with further decreases in ventricular function.⁹⁶ The cardiac protection that has been observed in the presence of volatile anesthetics may be related to protection from calcium overload associated with ischemia and reperfusion.⁹⁹

Treatment of cardiac dysrhythmias with calcium channel blockers in anesthetized patients produces only transient decreases in systemic blood pressure and infrequent prolongation of the P-R interval on the electrocardiogram. Because of the tendency to produce atrioventricular heart block, verapamil should be used cautiously in patients being treated with digitalis or β -adrenergic blocking drugs. Nevertheless, in patients with preoperative evidence of cardiac conduction abnormalities, the chronic combined administration of calcium channel blockers and β -adrenergic antagonists is not associated with cardiac conduction abnormalities in the perioperative period (**Table 19.8**).⁹⁴ β -Adrenergic agonists increase the number of functioning slow calcium channels in myocardial cell membranes through a cAMP mechanism and readily counter the effects of calcium channel blockers. Nevertheless, there is no evidence that patients being treated chronically with calcium channel blockers are at increased risk for anesthesia.

TABLE 19.8

Effect of chronic antianginal therapy on perioperative heart rate (beats per minute) and P-R interval (milliseconds)*

	Before induction	After induction	10 minutes after cardiopulmonary bypass
Control			
Heart rate	72	71	87
P-R interval	160	156	164
Calcium channel blockers			
Heart rate	69	70	86
P-R interval	168	169	175
β-Adrenergic antagonists			
Heart rate	59	65	78
P-R interval	168	171	183
Nifedipine plus β-adrenergic antagonists			
Heart rate	67	69	86
P-R interval	175	177	186

*Reprinted with permission from Henling CE, Slogoff S, Kodali SV, et al. Heart block after coronary artery bypass—effect of chronic administration of calcium-entry blockers and beta-blockers. *Anesth Analg*. 1984;63(5):515–520. Copyright © 1984 International Anesthesia Research Society.

Neuromuscular Blocking Drugs

Calcium channel blockers alone do not produce a skeletal muscle relaxant effect (**Figure 19.12**).¹⁰⁰ Conversely, these drugs do potentiate the effects of depolarizing and nondepolarizing neuromuscular blocking drugs (see **Figure 19.12**).^{100,101} This potentiation resembles that produced by mycin antibiotics in the presence of neuromuscular blocking drugs. The local anesthetic effects of verapamil and diltiazem, reflecting inhibition of sodium ion flux via fast sodium channels, may also contribute to the potentiation of neuromuscular blocking drugs. Observations of skeletal muscle weakness after administration of verapamil to a patient with muscular dystrophy are inconsistent with diminished release of neurotransmitter.¹⁰² Therefore, the neuromuscular effects of verapamil may be more likely to manifest in patients with a compromised margin of safety of neuromuscular transmission. There is no evidence that calcium channel blockers inhibit physical function in frail elderly patients.¹⁰³

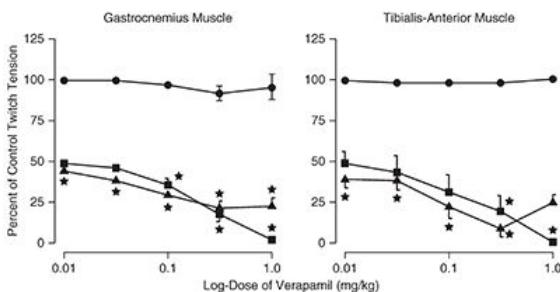


FIGURE 19.12 Infusion of verapamil in the absence of neuromuscular blocking drugs (solid circles) does not alter twitch height response (twitch tension) of indirectly stimulated rabbit skeletal muscle. When twitch tension is decreased to about 50% of control by the continuous infusion of pancuronium (solid squares) or succinylcholine (solid triangles), the addition of verapamil further decreases twitch tension. (The data points marked with “asterisk” represent a statistically significant decrease in muscle twitch tension as compared to verapamil alone. The errors represent the mean \pm standard error.) Reprinted with permission from Durant NN, Nguyen N, Katz RL. Potentiation of neuromuscular blockade by verapamil. Anesthesiology. 1984;60(4):298-303. Copyright © 1984 American Society of Anesthesiologists, Inc.

Potassium-Containing Solutions

Calcium channel blockers slow the inward movement of potassium ions. For this reason, hyperkalemia in patients being treated with verapamil may occur after much smaller amounts of exogenous potassium infusion as associated with the use of potassium chloride to treat hypokalemia or administration of stored whole blood.¹⁰⁴ In animals, however, pretreatment with verapamil does not alter the increases in plasma potassium concentrations that follow the administration of succinylcholine.¹⁰⁵

Platelet Function

Calcium channel blockers may interfere with calcium-mediated platelet function. In particular, there is an interaction between clopidogrel and calcium channel blockers related to their common metabolism by P450 enzyme 3A4. The conversion of the prodrug clopidogrel is reduced in the presence of calcium channel blockers, resulting in a fourfold increase in the risk of a composite outcome that included death related to cardiac causes, nonfatal myocardial infarction, stent thrombosis, and need for revascularization.¹⁰⁶

Digoxin

Calcium channel blockers increase the plasma concentration of digoxin, by decreasing its plasma clearance.¹⁰⁷

H₂ Antagonists

Cimetidine and ranitidine by altering hepatic enzyme activity and/or hepatic blood flow may increase the plasma concentrations of calcium channel blockers.

Cytoprotection

Drug-induced calcium channel blockade may provide cytoprotection against ischemic reperfusion injury.^{108,109} By decreasing calcium ion entry into cells and the conversion of xanthine dehydrogenase to xanthine oxidase (dependent on the calcium-calmodulin complex), calcium channel blockers may limit the accumulation of oxygen free radicals. Calcium channel blockers may attenuate renal injury from nephrotoxic drugs such as cisplatin and iodinated radiographic contrast media. The vasodilator effects of calcium channel blockers and resultant control of systemic hypertension may result in increases in renal blood flow and glomerular filtration rate, thus favoring natriuresis.

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Vasodilators*

Updated by: Thomas J. Krall • James Ramsay

Introduction

This chapter addresses the anesthetic implications of elevated blood pressure and the medications used to reduce systemic and pulmonary vascular pressures. As described in [Chapter 14](#), control of vascular tone in the peripheral and pulmonary circulations is a complex interplay of local metabolism, endothelial function, and regulation by the sympathetic nervous and endocrine systems.

Systemic Hypertension

The threshold for diagnosing hypertension was lowered in the 2017 American College of Cardiology/American Heart Association guidelines so that systemic hypertension is currently defined as a blood pressure of 130/80 to 139/89 mm Hg (stage 1) or greater than or equal to 140/90 mm Hg (stage 2).¹ This will raise the prevalence of hypertension in American adults from 30% to 45%, including 75% of those over 65 years of age.^{1,2} By far, the most common type of hypertension is “essential” or “primary” for which there is no clear unifying pathophysiology despite decades of research. What is clear, however, is that hypertension is a major risk factor for cardiovascular disease including atherosclerosis, heart failure, stroke, renal disease, and overall decreased survival.^{3,4} “Secondary” hypertension is much less common and can be due to a variety of causes ([Table 20.1](#)). Antihypertensive medications are used to control both primary and secondary hypertension. If more than three medications are required for consistent control, a diagnosis of secondary hypertension should be strongly suspected.

TABLE 20.1	
Systemic hypertension	
Essential (primary)	
Secondary	
Obstructive sleep apnea	
Renal disease	
Renal parenchymal disease	
Renal artery stenosis	
Endocrine disease	
Pheochromocytoma	
Primary aldosteronism	
Cushing disease	
Hyperparathyroidism	
Hyper- and hypothyroidism	
Medications	
Oral contraceptives	
Chronic NSAID use	
Antidepressants	
Alcohol	
Aortic coarctation	

Abbreviation: NSAID, nonsteroidal antiinflammatory drug.

Management of essential hypertension includes alteration in lifestyle and diet (smoking cessation, weight reduction, increased physical activity, salt restriction) and use of medications. Most commonly, a thiazide diuretic is the initial therapy as increased sodium excretion results in decreased blood pressure; these medications are inexpensive and require infrequent dosing. However, their chronic use requires potassium monitoring and supplementation.

Alternatively, monotherapy with a dihydropyridine calcium channel antagonist, such as amlodipine, or an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) may be used.⁵ Calcium channel blockade offers a direct vasodilator effect without the requirement of salt restriction and is associated with relatively few side effects. Use of an ACE inhibitor or ARB targets the renin-angiotensin system, a major contributor to blood pressure control. Decreased renal perfusion and increased sympathetic nervous system activity cause the release of renin, which then acts on “renin substrate” or angiotensin I at various sites in the body to release angiotensin II, a potent vasoconstrictor and promoter of sodium and water retention.⁶ Inhibition of angiotensin II production (with ACE inhibitor) or blockade of its receptor (with ARB) causes a reliable and potent antihypertensive effect, with very few side effects. In addition, in patients with most types of cardiac disease, these drugs have a well-known survival benefit. Although β -adrenergic blockade is also an option, they may be associated with inferior stroke protection (when compared to calcium channel blockade, ACE inhibitor, and ARB) in patients older than the age of 60 years⁷ and have a greater potential for systemic side effects.

Specific Antihypertensive Drugs and Anesthesia

Hypertensive patients are likely to be receiving one or more of thiazide diuretics, calcium channel blockers, ACE inhibitors/ARB medications, and β -adrenergic blockers. Less commonly, patients may be receiving other drugs, which antagonize the sympathetic nervous system (the centrally acting α_2 agonist clonidine, peripheral α_1 antagonists such as prazosin, α/β antagonists such as labetalol or carvedilol, nitrates, or hydralazine) (**Table 20.2**). Although many other drugs have been used in the past, they will not be discussed here. In general, antihypertensive therapy should be continued until the time of surgery, as managing poorly controlled hypertension is likely to be more difficult than managing the well-controlled hypertensive patient. Specific recommendations for withholding ACE inhibitors or angiotensin receptor blockers are discussed later. Severe or poorly controlled hypertension is a relatively common cause for postponement of surgery,⁸ although evidence supporting this practice comes from small studies mostly more than 20 years old. Although there is an association between uncontrolled blood pressure and adverse cardiovascular events, it remains unclear if postponing surgery for blood pressure control improves outcomes.⁹ Specific drugs and implications for perioperative management are discussed in the following text.

TABLE 20.2

Intravenous antihypertensive drugs commonly used in the perioperative setting

Drug	Mechanism	Intravenous dosing		Onset (minutes)	Duration plasma half-life clinical effect ^a
		Bolus	Infusion		
Metoprolol	β_1 Blocker	1-5 mg	N/A	1-5	Half-life: 3-7 hours Clinical: 1-4 hours
Labetalol	α_1 , β_1 , β_2 Blocker	5-20 mg	0.5-2 mg per minute	1-5	Half-life: 6 hours Clinical: 1-4 hours
Esmolol	β_1 Blocker	500-1,000 μ g/kg	50-300 μ g/kg per minute	1-2	Half-life: 9 minutes
Nicardipine	Dihydropyridine Ca blocker	100-400 μ g	5-15 mg per hour	2-10	Half-life: 2-4 hours Clinical: 30-60 minutes
Clevidipine (infusion only)	Dihydropyridine Ca blocker	N/A	1-16 mg per hour ^b	2-4	Half-life: 1 minute Clinical: 5-15 minutes
Hydralazine	Arteriolar dilator	5-20 mg	N/A	5-20	Half-life: 2-8 hours Clinical: 1-8 hours
Fenoldopam	Dopamine type 1 agonist	N/A	0.05-1.6 μ g/kg per minute	5-10	Half-life: 5 minutes Clinical: 30-60 minutes
Nitroprusside	NO donor	N/A	0.25-4 μ g/kg per minute	1-2	Half-life: <10 minutes Clinical: 1-10 minutes

Nitroglycerin	NO donor	20-400 µg	10-400 µg per minute	1-2	Half-life: 1-3 minutes Clinical: 5-10 minutes
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Abbreviations: Ca, calcium; NO, nitric oxide.

^aClinical effect commonly seen after bolus dose or stopping infusion.

^bUsual clinical range 4-6 mg per hour; see manufacturer's dosing algorithms.

β-Adrenergic Blockers

As mentioned earlier, β blockers are less commonly used as first-line agents in hypertension as other agents may have a better safety profile for this indication in those older than the age of 60 years. In addition, β blockers have a potential side effect profile, which limits their use in many patients including fatigue, depression, and impotence. However, β blockers are indicated for long-term treatment of patients with coronary artery disease and heart failure, in addition to their antihypertensive action.

Mechanism of Action

β Blockers can be classified according to whether they exhibit β₁ selective versus nonselective properties and whether they possess intrinsic sympathomimetic activity. A β blocker with selective properties binds primarily to β₁ (cardiac) receptors, whereas a β blocker with nonselective properties has equal affinity for β₁ and β₂ (vascular and bronchial smooth muscle, metabolic) receptors. The β blockers with intrinsic sympathomimetic activity (pindolol, acebutolol) tend to produce less bradycardia and thus are less likely to unmask left ventricular dysfunction. These drugs are also less likely to produce vasospasm and thus to exacerbate symptoms of peripheral vascular disease. The antihypertensive effect of β blockers and other vasodilators may be attenuated by nonsteroidal antiinflammatory drugs.¹⁰

In contrast to nonselective β blockers such as propranolol, cardioselective β₁ blockers (acebutolol, atenolol, metoprolol, bisoprolol) administered in low to moderate doses are unlikely to produce bronchospasm, decrease peripheral blood flow, or mask hypoglycemia. For these reasons, they are the preferred drugs for patients with pulmonary disease, insulin-dependent diabetes mellitus, or symptomatic peripheral vascular disease. The nonselective agent carvedilol, which also has α₁ blocking action, has been shown to improve survival in patients with systolic heart failure.¹¹⁻¹³ The cardioselective drugs metoprolol and bisoprolol have also been shown to provide a survival benefit in this population.¹⁴ A randomized trial of carvedilol versus metoprolol in heart failure suggested a mortality benefit for carvedilol, although the study was critiqued for potentially underdosing the metoprolol arm.¹⁵ Labetalol is another nonselective β blocker that also has significant α₁ blocking action. The presence of α-adrenergic blocking properties results in less bradycardia and negative inotropic effects compared with “pure” β blockers. These α properties, however, may result in orthostatic hypotension. The incidence of bronchospasm is similar to that seen with atenolol or metoprolol. Intravenous (IV) labetalol is used in hypertensive emergencies and is particularly useful in managing patients with type B aortic dissections, facilitating conversion from IV to oral medications.

Side Effects

Treatment of hypertension with β blockers involves certain risks, including bradycardia and heart block, congestive heart failure, bronchospasm, claudication, masking of hypoglycemia, sedation, and impotence, and when abruptly discontinued may precipitate angina pectoris or even myocardial infarction. Patients with any degree of congestive heart failure cannot generally tolerate more than modest doses of β blockers; yet, it is clear that when dosage is slowly increased and the drugs are given chronically, the antiadrenergic effect provides a significant benefit in chronic systolic heart failure.¹¹⁻¹⁵ Nonselective β blockers should likely be avoided in symptomatic asthma, although recent data suggests that selective β blockers are likely safe in asthma¹⁶ and chronic obstructive pulmonary disease^{17,18} and should be continued during chronic obstructive pulmonary disease exacerbations.¹⁹ β Blockers potentially increase the risk of serious hypoglycemia in diabetic patients because they blunt autonomic nervous system responses that would warn of hypoglycemia.

Nevertheless, the incidence of hypoglycemia has not been shown to be increased in diabetic patients being treated with β -adrenergic antagonists to control hypertension.²⁰

Intravenous β Blockers

The IV β blockers available in North America include metoprolol, propranolol, labetalol (an α_1 /nonselective β blocker), and esmolol, which is a very short-acting cardioselective agent, inactivated by plasma esterases. Perioperative β blockade can be used to continue preoperative therapy, but due to extensive first-pass activity for oral agents, the conversion to IV dosing is somewhat unpredictable. In the case of labetalol, its $\beta:\alpha$ ratio is 3:1 when taken orally and 7:1 when given IV.²¹

α_1 Receptor Blockers

Prazosin, terazosin, and doxazocin are oral, selective postsynaptic α_1 -adrenergic receptor antagonists resulting in vasodilating effects on both arterial and venous vasculature. Absence of presynaptic α_2 receptor antagonism leaves intact the normal inhibitory effect on norepinephrine release from nerve endings. These drugs are unlikely to elicit reflex increases in cardiac output and renin release. In contrast, oral phenoxybenzamine and IV phentolamine are nonselective α blockers, which also block presynaptic α_2 receptors. Both of these drugs are used almost exclusively in the management of pheochromocytoma and are not be discussed further. Urapidil is a potent α_1 antagonist and centrally acting serotonin antagonist, which is available outside the United States in both oral and IV formulations.

In addition to treating essential hypertension, prazosin may be of value for decreasing afterload in patients with congestive heart failure. Prazosin may also be a useful drug for the preoperative preparation of patients with pheochromocytoma. This drug has been used to relieve the vasospasm of Raynaud phenomenon. Another useful indication for prazosin in the treatment of essential hypertension is the presence of benign prostatic hypertrophy in older males, as this drug decreases the size of the gland.²²

Pharmacokinetics

Prazosin is nearly completely metabolized, and less than 60% bioavailability after oral administration suggests the occurrence of substantial first-pass hepatic metabolism. The elimination half-time is about 3 hours and is prolonged by congestive heart failure but not renal dysfunction. The fact that this drug is metabolized in the liver permits its use in patients with renal failure without altering the dose.

Cardiovascular Effects

Prazosin decreases systemic vascular resistance without causing reflex-induced tachycardia or increases in renin activity as occurs during treatment with hydralazine or minoxidil. Failure to alter plasma renin activity reflects continued activity of α_2 receptors that normally inhibit the release of renin. Vascular tone in both resistance and capacitance vessels is decreased, resulting in decreased venous return and cardiac output.

Side Effects

The side effects of prazosin include vertigo, fluid retention, and orthostatic hypotension. Nonsteroidal antiinflammatory drugs may interfere with the antihypertensive effect of prazosin. Dryness of the mouth, nasal congestion, nightmares, urinary frequency, lethargy, and sexual dysfunction may accompany treatment with this drug. Hypotension during epidural anesthesia may be exaggerated in the presence of prazosin, reflecting drug-induced α_1 blockade that prevents compensatory vasoconstriction in the unblocked portions of the body.²³ The resulting decrease in systemic vascular resistance results in hypotension that may not be responsive to the usual clinical doses of an α_1 -adrenergic agonist such as phenylephrine. In this situation, administration of epinephrine may be necessary to increase systemic vascular resistance and systemic blood pressure. Conceivably, the combination of prazosin and a β blocker could result in particularly refractory hypotension during regional anesthesia due to potentially blunted responses to β_1 as well as α_1 agonists.

α_2 Agonists

Clonidine is a centrally acting selective partial α_2 -adrenergic agonist (220:1 α_2 to α_1 activity) that acts as an antihypertensive drug by virtue of its ability to decrease sympathetic output from the central nervous system (CNS). This drug has proved to be particularly effective in the treatment of patients with severe hypertension or renin-dependent disease. The usual daily adult dose is 0.2 to 0.3 mg orally. The availability of a transdermal clonidine patch designed for weekly administration is a more convenient formulation but is not useful in the acute setting as the onset is slow (hours). Another drug of the same class is IV dexmedetomidine, a much more α_2 -selective drug that is approved for sedation rather than hypertension, although it does have a blood pressure–lowering action. Dexmedetomidine is discussed in [Chapter 5](#).

Mechanism of Action

α_2 -Adrenergic agonists produce clinical effects by binding to α_2 receptors of which there are three subtypes (α_{2A} , α_{2B} , α_{2C}) that are distributed ubiquitously, and each may be uniquely responsible for some, but not all, of the actions of α_2 agonists ([Figure 20.1](#)).²⁴ α_{2A} Receptors mediate sedation, analgesia, and sympatholysis, whereas α_{2B} receptors mediate vasoconstriction and possibly antishivering effects. The startle response may reflect activation of α_{2C} receptors.

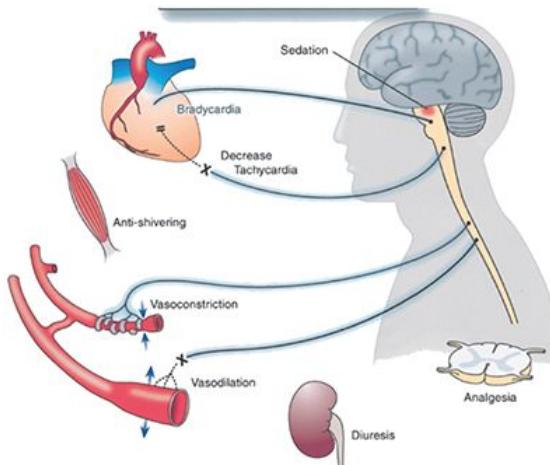


FIGURE 20.1 Schematic depiction of effects that are mediated by α_2 -adrenergic receptors. The site for sedation is the locus ceruleus of the brainstem, whereas the principal site of analgesia is most likely the spinal cord. In the heart, the dominant effect of α_2 stimulation is attenuation of tachycardia through block of the cardioaccelerator nerves and bradycardia through vagal stimulation. In the peripheral vasculature, there are vasodilatory effects reflecting sympatholysis and vasoconstriction mediated by α_2 receptors in smooth muscle cells. *Reprinted with permission from Kamibayashi T, Maze M. Clinical uses of alpha2-adrenergic agonists. Anesthesiology. 2000;93(5):1345-1349. Copyright © 2000 American Society of Anesthesiologists, Inc.*

Clonidine stimulates α_2 -adrenergic inhibitory neurons in the medullary vasomotor center. As a result, there is a decrease in sympathetic nervous system outflow from CNS to peripheral tissues. Decreased sympathetic nervous system activity is manifested as peripheral vasodilation and decreases in systemic blood pressure, heart rate, and cardiac output. The ability of clonidine to modify the function of potassium channels in the CNS (cell membranes become hyperpolarized) may be the mechanism for profound decreases in anesthetic requirements produced by clonidine and other even more selective α_2 -adrenergic agonists such as dexmedetomidine. α_2 Receptors on blood vessels mediate vasoconstriction and inhibit release of norepinephrine on peripheral sympathetic nervous system nerve endings. Neuraxial placement of clonidine inhibits spinal substance P release and nociceptive neuron firing produced by noxious stimulation.

Pharmacokinetics

Clonidine is rapidly absorbed after oral administration and reaches peak plasma concentrations within 60 to 90 minutes. The elimination half-time of clonidine is between 9 and 12 hours, with approximately 50% metabolized in the liver, whereas the rest is excreted unchanged in urine. The duration of hypotensive effect after a single oral dose is about 8 hours. The transdermal route requires about 48 hours to produce steady-state therapeutic plasma concentrations.

Cardiovascular Effects

The decrease in systolic blood pressure produced by clonidine is more prominent than the decrease in diastolic blood pressure. In patients treated chronically, systemic vascular resistance is little affected, and cardiac output, which is initially decreased, returns toward predrug levels. Homeostatic cardiovascular reflexes are maintained, thus avoiding the problems of orthostatic hypotension or hypotension during exercise. The ability of clonidine to decrease systemic blood pressure without paralysis of compensatory homeostatic reflexes is highly desirable. Renal blood flow and glomerular filtration rate are maintained in the presence of clonidine therapy.

Side Effects

The most common side effects produced by clonidine are sedation and xerostomia. Consistent with sedation and, perhaps more specifically, an agonist effect on postsynaptic α_2 receptors in the CNS are nearly 50% decreases in anesthetic requirements for inhaled anesthetics (minimum alveolar concentration) and injected drugs in patients pretreated with clonidine administered in the preanesthetic medication.²⁵ Patients pretreated with clonidine often manifest lower plasma concentrations of catecholamines in response to surgical stimulation and occasionally require treatment of bradycardia. As with other antihypertensive drugs, retention of sodium and water often occurs such that combination of clonidine with a diuretic is often necessary. Conversely, a diuretic effect during general anesthesia has been described after administration of oral clonidine, 2.5 to 5.0 $\mu\text{g}/\text{kg}$ as preanesthetic medication.²⁶ Skin rashes are frequent, impotence occurs occasionally, and orthostatic hypotension is rare. Despite the fact that clonidine prevents opioid-induced skeletal muscle rigidity and produces skeletal muscle flaccidity, α_2 agonists have no effect on the responses evoked by neuromuscular blocking drugs.²⁷

Rebound Hypertension

Abrupt discontinuation of clonidine therapy can result in rebound hypertension as soon as 8 hours and as late as 36 hours after the last dose.²⁸ Rebound hypertension is most likely to occur in patients who were receiving greater than 1.2 mg of clonidine daily. The increase in systemic blood pressure may be associated with a greater than 100% increase in circulating concentrations of catecholamines and intense peripheral vasoconstriction. Symptoms of nervousness, diaphoresis, headache, abdominal pain, and tachycardia often precede the actual increase in systemic blood pressure. β -Adrenergic blockade may exaggerate the magnitude of rebound hypertension by blocking the β_2 vasodilating effects of catecholamines and leaving unopposed their α vasoconstricting actions. Likewise, tricyclic antidepressant therapy may exaggerate rebound hypertension associated with abrupt discontinuation of clonidine therapy.²⁹ Tricyclic antidepressants can potentiate the pressor effects of norepinephrine.

Rebound hypertension can usually be controlled by reinstituting clonidine therapy or by administering a vasodilating drug such as hydralazine or nitroprusside. β -Adrenergic blocking drugs are useful but probably should be administered only in the presence of α -adrenergic blockade to avoid unopposed α vasoconstricting actions. In this regard, labetalol with α and β antagonist effects may be useful in the management of patients experiencing rebound hypertension. If oral clonidine therapy is interrupted because of surgery, use of transdermal clonidine provides a sustained therapeutic level of drug for as long as 7 days.³⁰ For a planned withdrawal, the clonidine dosage should be gradually decreased over 7 days or longer.

Rebound hypertension after abrupt discontinuation of chronic treatment with antihypertensive drugs is not unique to clonidine.²⁸ For example, abrupt discontinuation of β blocker therapy has been associated with

clinical evidence of excessive sympathetic nervous system activity. Antihypertensive drugs that act independently of central and peripheral sympathetic nervous system mechanisms (direct vasodilators, ACE inhibitors) do not seem to be associated with rebound hypertension after sudden discontinuation of therapy.

Other Clinical Uses

α -Adrenergic agonists (clonidine and dexmedetomidine) induce sedation, decrease anesthetic requirements, and improve perioperative hemodynamic (attenuate blood pressure and heart rate responses to surgical stimulation) and sympathoadrenal stability.²⁴ Although a number of small studies have demonstrated these benefits, the Perioperative Ischemic Evaluation 2 trial (2014) failed to demonstrate a cardioprotective effect when used perioperatively.³¹ The trial randomized patients in a 2-by-2 design to test the effect of low-dose clonidine (0.2 mg per day) versus placebo and low-dose aspirin (100 mg daily) versus placebo. The clonidine was started preoperative and continued for 72 hours after surgery. They found no change in the primary composite outcome of death and nonfatal myocardial infarction, but they found an increase in hypotension and nonfatal cardiac arrest in the clonidine group. Both clonidine and dexmedetomidine have been used to help reduce the sympathetic nervous system hyperactivity associated with alcohol and opioid withdrawal. α_2 Receptors within the spinal cord modulate pain pathways resulting in analgesia, and intrathecal clonidine has been studied as an effective adjuvant to neuraxial blockade both enhancing and prolonging sensory and motor block.

Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers

The ACE inhibitors represented a major advance in the treatment of all forms of hypertension because of their potency and minimal side effects, resulting in improved patient compliance.³² The ARBs provide a similar mechanism of action with a slightly better side effect profile. These drugs are free of many of the CNS side effects associated with other antihypertensive drugs, including depression, insomnia, and sexual dysfunction. Other adverse effects, such as congestive heart failure, bronchospasm, bradycardia, and exacerbation of peripheral vascular disease, are not seen with ACE inhibitors/ARBs either. Similarly, metabolic changes induced by diuretic therapy, such as hypokalemia, hyponatremia, and hyperglycemia, are not observed. Rebound hypertension, as seen with clonidine, has also not been observed with ACE inhibitors/ARBs.

The ACE inhibitors are most effective in treating systemic hypertension secondary to increased renin production. These drugs have been established as first-line therapy in patients with systemic hypertension, congestive heart failure, and mitral regurgitation. The ACE inhibitors are more effective and possibly safer than other antihypertensive drugs in the treatment of hypertension in diabetics.³³ There is also evidence that ACE inhibitors delay the progression of diabetic renal disease.³⁴ As mentioned earlier, ACE inhibitors have been shown to provide a survival benefit in patients who have suffered a myocardial infarction and in patients with heart failure.³⁵

Mechanism of Action

Angiotensin II normally binds to a specific cell membrane receptor (AT_1) that ultimately leads to increased release of calcium from sarcoplasmic reticulum to produce vasoconstriction. Decreased generation of angiotensin II due to the administration of an ACE inhibitor results in reduced vasoconstrictive effects. In addition, plasma concentrations of aldosterone are decreased resulting in less sodium and water retention. The ACE inhibitors also block the breakdown of bradykinin, an endogenous vasodilator substance, which contributes to the antihypertensive effects of these drugs. The ACE inhibitors, like statins, reduce activation of low-density lipoprotein (LDL) receptors and thus decrease plasma concentrations of LDL cholesterol. If the concentration of LDL cholesterol is already sufficiently low, ACE inhibitors may no longer be effective in reducing the rate of cardiovascular events.³⁶

The ACE inhibitors can be classified according to the structural element that interacts with the zinc ion of the enzyme as well as the form in which the drug is administered (prodrug or active form). Administration of ACE inhibitors as prodrugs increases oral bioavailability prior to their hepatic metabolism to the active

drug. Enalapril is the prodrug of the active ACE inhibitor, enalaprilat, and conversion may be altered in patients with hepatic dysfunction. Captopril and lisinopril are not prodrugs. The major difference among clinically used ACE inhibitors is in duration of action.³⁷ The ARBs produce antihypertensive effects by blocking the vasoconstrictive actions of angiotensin II without affecting ACE activity.

Side Effects

Cough, upper respiratory congestion, rhinorrhea, and allergic-like symptoms seem to be the most common side effects of ACE inhibitors.³⁸ It is speculated that these airway responses reflect potentiation of the effects of kinins due to drug-induced inhibition of peptidyl-dipeptidase activity and subsequent breakdown of bradykinin. If respiratory distress develops, prompt injection of epinephrine (0.3-0.5 mL of a 1:1,000 dilution subcutaneously) is advised. Angioedema is a potentially life-threatening complication of treatment with ACE inhibitors. Decreases in glomerular filtration rate may occur in patients treated with ACE inhibitors. For this reason, ACE inhibitors are used with caution in patients with preexisting renal dysfunction and are not recommended for patients with renal artery stenosis. Hyperkalemia is possible due to decreased production of aldosterone. The risk of hyperkalemia is greatest in patients with recognized risk factors (congestive heart failure with renal insufficiency).³⁹ Measurement of plasma concentrations of potassium may be indicated in these patients.

The ARBs have similar side effect profile but do not inhibit breakdown of bradykinin, one of the benefits of ACE inhibitors and which may be a reason that ACE inhibitors are generally preferred as first-line therapy. A major difference between ACE inhibitors and ARBs is that ARBs do not cause cough, one of the reasons ACE inhibitors may not be tolerated (more than 10% of patients).

Preoperative Management

Adverse circulatory effects during anesthesia are recognized in patients chronically treated with ACE inhibitors/ARBs leading some to recommend that these drugs be discontinued 12 to 24 hours before anesthesia and surgery.⁴⁰ A retrospective study of more than 75,000 patients (9,900 taking ACE inhibitors) suggested that although continuation of these drugs until the time of surgery is associated with more intraoperative hypotension, there were no adverse consequences.⁴¹ A 2018 meta-analysis that included ACE inhibitors and ARBs also drew similar conclusions: Withholding ACE inhibitors/ARBs prior to surgery resulted in less intraoperative hypotension, but no change in mortality or major adverse cardiac events.⁴² However, a large data set of noncardiac surgery patients (Vascular Events in Non-cardiac Surgery Patients Cohort Evaluation Study [VISION]—a prospective study of 16,000 patients in eight countries) showed an association with same-day ACE inhibitors/ARB administration and increased mortality and major adverse events.⁴³ Currently, the 2014 American College of Cardiology/American Heart Association guidelines for perioperative management suggests it is “reasonable” to continue these drugs until the time of surgery, although many anesthesia practice groups hold them to avoid the hypotensive effects.⁴⁴ Exaggerated hypotension attributed to continued ACE inhibitor therapy has been responsive to crystalloid fluid infusion and/or administration of a catecholamine or vasopressin infusion. The ACE inhibitors may increase insulin sensitivity and hypoglycemia, which is a concern when these drugs are administered to patients with diabetes mellitus. Nevertheless, there is no evidence that the incidence of hypoglycemia is greater in diabetics being treated with ACE inhibitors for control of hypertension.²⁰

Specific Agents

Perioperative implications of different ACE inhibitors are similar; it is not clear that any one agent has more or less effect on perioperative blood pressure control. The only IV ACE inhibitor is enalaprilat; however, there is little published information to guide its use in this setting. It is not used as an infusion (ie, dosing recommendations are for intermittent injection) and has a less predictable onset and duration of action as well as antihypertensive action than short-acting direct vasodilators. Oral agents commonly seen are captopril, enalapril, lisinopril, and ramipril with the latter agents having a longer duration of action than captopril.

Common ARBs include losartan, irbesartan, candesartan, olmesartan, and valsartan, all of which have a relatively long duration of action (one or twice daily dosing). There is no IV agent available. These agents have similar antihypertensive actions and benefits in patients with heart failure as ACE inhibitors, although the evidence is somewhat less robust. A new combination of a neprilysin inhibitor with valsartan (sacubitril/valsartan) showed lower rates of death or hospitalization for heart failure in patients with ejection fraction less than 40%.⁴⁵ Neprilysin is a circulating enzyme that metabolizes vasoactive peptides, including bradykinin, enkephalins, substance P, and the natriuretic peptides. The increase in circulating natriuretic peptide levels may explain the clinical benefit in heart failure.⁴⁶ This medication will likely see increased utilization of the coming years for heart failure patients.

Calcium Channel Blocking Drugs

Calcium channel blocking drugs used as antihypertensives inhibit calcium influx through the voltage-sensitive L-type calcium channels in vascular smooth muscle. They are arterial specific, with little effect on venous circulation. The calcium channel drugs are broadly categorized into drugs of the dihydropyridine class (nifedipine, amlodipine, nicardipine, clevidipine) and those of the nondihydropyridine class (verapamil and diltiazem). Verapamil and diltiazem are less potent vasodilators and both have negative inotropic and chronotropic activity limiting their use in patients with cardiac disease. In current practice, these drugs are more used for their antiarrhythmic action than antihypertensive action (see [Chapter 21](#)).

The dihydropyridines are potent vasodilators and are relatively safe to use in patients with heart failure and cardiac conduction defects, with the exception of large doses of short-acting nifedipine, which may acutely lower the blood pressure and cause myocardial ischemia. The use of calcium channel blockers does not require concurrent sodium restriction, which makes these drugs unique antihypertensive drugs and perhaps the drugs of choice for patients who find sodium restriction unacceptable. The once-daily dosing of amlodipine is of particular appeal.

The parenteral dihydropyridine calcium channel blockers nicardipine and clevidipine are available as continuous IV infusions. They both offer rapid titration and short half-lives. The use of IV nicardipine in the perioperative setting is well studied, and it also has been used in the treatment of hypertensive emergencies.⁴⁷ Nicardipine undergoes hepatic metabolism and therefore showed elevated plasma concentrations and prolonged half-life in hepatic impairment. Clevidipine offers an advantage of being metabolized by plasma esterases to inactive metabolites. Its dosing does not require adjustment in the setting of hepatic or renal dysfunction. Its rapid titration, end-organ independent metabolism, and good safety profile has led to increased study of clevidipine in the critical care and perioperative environment, where it performs comparably to nicardipine.^{48–52} In a randomized trial of clevidipine compared to nitroglycerin, sodium nitroprusside (SNP), and nicardipine in perioperative cardiac surgery, patients spent statistically significantly less time outside of a prespecified blood pressure range with clevidipine than with SNP or nitroglycerin. The performance of clevidipine was equal to nicardipine on that metric. There was no significant difference in any adverse event rates for the four drugs.⁵¹ Clevidipine appears to be a potent and safe alternative to existing parenteral vasodilators.

Clevidipine and nicardipine share adverse effect profiles with the other dihydropyridine calcium channel blockers, including potential reflex tachycardia and negative inotropy. Potent vasodilators are known to inhibit hypoxic pulmonary vasoconstriction, and the parenteral calcium channel blockers are no exception.^{53,54} There are limited case reports of hypoxemia in the setting of nicardipine or clevidipine administration.^{55,56} This phenomenon is not completely understood but appears to involve inhibition of hypoxic pulmonary vasoconstriction in the setting of existing lung pathology leading to worsened ventilation-perfusion matching. The anesthesiologist should be aware of this phenomenon because of its rapid reversibility with discontinuation of these short-acting drugs. Clevidipine is an injectable lipid emulsion and is contraindicated in patients with defective lipid metabolism. Its similar visual appearance to propofol warrants special handling caution. Clevidipine is relatively contraindicated in severe aortic stenosis due to the potential for lowering coronary perfusion pressure and precipitating myocardial ischemia.⁵⁷

Phosphodiesterase Inhibitors

The phosphodiesterases (PDEs) are a broad family of 11 isoenzymes, which variably mediate the breakdown of intracellular cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP).⁵⁸ Although the many noncardiovascular actions of these enzymes are beyond the scope of this chapter, drugs of this class likely to be encountered by the anesthesiologist include the PDE3 inhibitors amrinone and milrinone and the PDE5 inhibitors sildenafil, tadalafil, and vardenafil. Inhibition of PDE causes vascular smooth muscle relaxation and, in the case of PDE3 inhibitors, positive inotropy from intracellular calcium mobilization.

The IV PDE3 inhibitor milrinone has replaced amrinone due to its reduced side effect profile. Breakdown of both cAMP and cGMP are inhibited in myocardial cells and vascular smooth muscle by this enzyme. Its combined inotropic and vasodilator actions make it a beneficial drug in the short-term treatment of heart failure, both in the intensive care and operative settings. An extensive literature documents its short-term hemodynamic benefits, whereas long-term oral use was associated with cardiovascular adverse effects and increased mortality. Although milrinone would not be a first-choice IV vasodilator in the absence of cardiac dysfunction, its vasodilation actions provide a significant benefit in the setting of heart failure. Milrinone is excreted by the kidneys mostly as unchanged drug. It has a half-life of 2 to 4 hours with normal renal function. The half-life increases in kidney injury, up to roughly 20 hours in a patient on continuous renal replacement therapy.⁵⁹

The PDE5 inhibitors selectively inhibit the breakdown of cGMP, more in vascular smooth muscle than in other cardiovascular sites. Due to a high level of PDE5 in the lungs, these drugs are effective pulmonary vasodilators, and they are also effective for erectile dysfunction. They are only available in oral formulations. Although peripheral (systemic) vascular effects are modest, when combined with other vasodilators, there can be significant lowering of blood pressure. Concurrent administration of nitroglycerin and erectile dysfunction drugs within 24 hours is not recommended as life-threatening hypotension from exaggerated systemic vasodilation may occur.⁶⁰

Nitric Oxide and Nitrovasodilators

Nitric Oxide

Nitric oxide (NO) is recognized as a chemical messenger in a multitude of biologic systems, with homeostatic activity in the modulation of cardiovascular tone (see [Chapter 14](#)), platelet regulation, and a neurotransmitter function in the CNS. In addition, it has roles in gastrointestinal smooth muscle relaxation and immune regulation. Therapeutically, NO is administered by inhalation to produce relaxation of the pulmonary arterial vasculature.

The NO is synthesized in endothelial cells from the amino acid L-arginine by NO synthetase, a constitutively expressed enzyme. It then diffuses into precapillary resistance arterioles where it induces guanylate cyclase to increase the cGMP concentration, which in turn results in vasodilation. It is formerly known as “endothelial-derived relaxing factor.” The NO production has a large role in regulation of vascular tone throughout the body. There is evidence to support deficiency in NO production being related to various vascular diseases including essential hypertension. As a result of stress, an inducible form of NO synthetase can produce large amounts of NO contributing to excessive vasodilation. The NO binds to the iron of heme-based proteins and thus is avidly bound and inactivated by hemoglobin leading to a half-time of less than 5 seconds under normal physiologic conditions.

As a therapeutic agent, inhaled NO affects the pulmonary circulation but not the systemic circulation due to its extremely rapid uptake by hemoglobin. Nitrovasodilators (nitrates and nitroprusside) work through generation of NO (see the following discussion) throughout the vasculature.

Nitric Oxide as a Pulmonary Vasodilator

Inhaled NO causes pulmonary arterial vasodilation that is proportional to the degree of pulmonary vasoconstriction ([Figure 20.2](#)). It has less effect on pulmonary vascular resistance if pulmonary vascular tone is not increased such as in types of pulmonary hypertension other than “primary.” By dilating vessels in

alveoli where it is locally delivered, inhaled NO usually improves oxygenation by improving ventilation-perfusion matching.

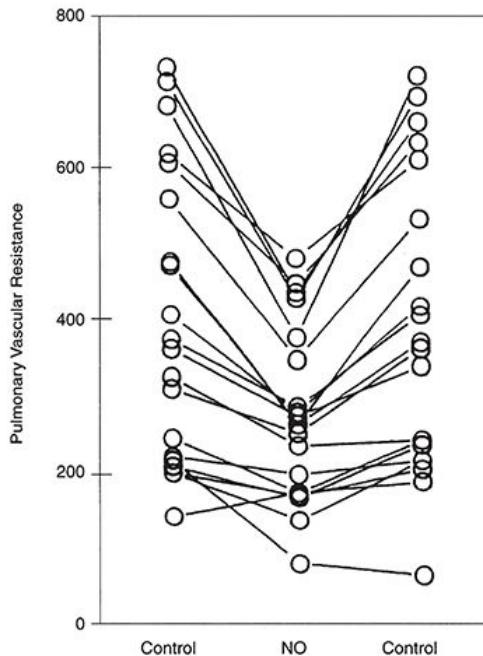


FIGURE 20.2 Inhalation of nitric oxide (NO). Pulmonary vascular resistance ($\text{dyne}/\text{cm}/\text{s}^{-5}$) before, during, and after inhalation of NO for each patient before cardiopulmonary bypass. Reprinted with permission from Rich GF, Murphy GD Jr, Roos CM, et al. Inhaled nitric oxide: selective pulmonary vasodilation in cardiac surgical patients. *Anesthesiology*. 1993;78(6):1028-1035. Copyright © 1993 American Society of Anesthesiologists, Inc.

In the United States, the only approved indication for inhaled NO is in pediatric lung injury. Inhaled NO, 10 to 20 ppm, has been used for therapy of persistent pulmonary hypertension of the newborn.^{61,62} Inhalation of NO in premature infants with respiratory distress syndrome decreases the incidence of chronic lung disease and death.⁶³

In the adult population, NO is used “off label” in managing severe pulmonary hypertension especially in the setting of acute right heart dysfunction or failure and in perioperative management of heart and lung transplant recipients. In acute lung injury and acute respiratory distress syndrome, inhaled NO will often provide a modest improvement in pulmonary hemodynamics and oxygenation, but clinical trials have failed to demonstrate an outcome benefit in this setting.⁶⁴

Toxicity

Inhaled NO increases methemoglobin levels as NO combines with hemoglobin. The increases in methemoglobin concentrations are usually modest. Life-threatening rebound arterial hypoxemia and pulmonary hypertension may accompany discontinuation of inhaled NO therapy.⁶⁵ Because of the variability in rebound pulmonary hypertension, it is important to wean patients from inhaled NO slowly. The NO is oxidized to nitrogen dioxide (NO_2) especially in the presence of high concentrations of oxygen. The NO_2 is a known pulmonary toxin (“silo-filler’s disease”) and is a possible product of the interaction of NO with oxygen. It is conceivable that NO_2 concentrations could produce pulmonary toxicity during treatment with NO. Continuous monitoring of inspired NO and NO_2 concentrations provided in the current delivery system is important to provide an early warning of possible pulmonary toxicity. In the presence of left heart dysfunction or failure, the increased pulmonary blood flow caused by inhaled NO can precipitate acute left heart failure and pulmonary edema.

Nitrodilators

The SNP and IV nitroglycerin are historically the vasodilators most widely used by anesthesiologists. As described earlier, these agents work through the generation of NO, which then augments cGMP in vascular smooth muscle, both arteries and veins, leading to vasodilation. The more recent availability of IV nicardipine and other arterial-specific dilators such as clevidipine and fenoldopam has to some degree replaced the use of the nitrodilators, especially nitroprusside due to its potential toxicities discussed later.

Sodium Nitroprusside

An SNP is a direct-acting, nonselective peripheral vasodilator that causes relaxation of arterial and venous vascular smooth muscle.⁶⁶ It is composed of a ferrous ion center complexed with five cyanide (CN^-) moieties and a nitrosyl group. The molecule is 44% cyanide by weight and is soluble in water. The SNP lacks significant effects on nonvascular smooth muscle and on cardiac muscle. Its onset of action is almost immediate, equipotent on arteries and veins, and its duration is transient, requiring continuous IV administration to maintain a therapeutic effect. The extreme potency of SNP necessitates careful titration of dosage as provided by continuous infusion devices and frequent monitoring of systemic blood pressure, often by intra-arterial monitoring.

Mechanism of Action

When infused IV, SNP interacts with oxyhemoglobin, dissociating immediately and forming methemoglobin while releasing cyanide and NO.⁶⁶ Once released, NO activates the enzyme guanylate cyclase present in vascular smooth muscle, resulting in increased intracellular concentrations of cGMP.⁶⁶ The cGMP inhibits calcium entry into vascular smooth muscle cells and may increase calcium uptake by the smooth endoplasmic reticulum to produce vasodilation.⁶⁷ As such, NO is the active mediator responsible for the direct vasodilating effect of SNP. In contrast to the organic nitrates (nitroglycerin), which require the presence of thio-containing compounds to generate NO, SPN spontaneously generates this product, thus functioning as a prodrug.

Metabolism

Metabolism of SNP begins with the transfer of an electron from the iron of oxyhemoglobin to SNP, yielding methemoglobin and an unstable SNP radical.⁶⁶ This electron transfer is independent of electron activity. The unstable SNP radical promptly breaks down, releasing all five cyanide ions, one of which reacts with methemoglobin to form cyanomethemoglobin. The remaining free cyanide ions are available to rhodanese enzymes in the liver and kidneys for conversion to thiocyanate. Rhodanese uses thiosulfate ions as sulfur donors, and most adults can detoxify approximately 50 mg of SNP using existing sulfur stores. Normal adult methemoglobin concentrations (about 0.5% of all hemoglobin) are capable of binding the cyanide released from 18 mg of SNP. Cyanomethemoglobin remains in dynamic equilibrium with free cyanide and is nontoxic. The nonenzymatic release of cyanide from SNP is not inhibited by hypothermia as may be present during cardiopulmonary bypass, whereas enzymatic conversion of cyanide to thiocyanate may be delayed.⁶⁸

Dose and Administration

Patients receiving SNP should have blood pressure monitored continuously via an arterial catheter. The recommended initial dose of SNP is 0.3 $\mu\text{g}/\text{kg}$ per minute IV titrated to a maximum rate of 10 $\mu\text{g}/\text{kg}$ per minute IV, with the maximum rate not to be infused longer than 10 minutes.⁶⁹ The SNP infusion rates of greater than 2 $\mu\text{g}/\text{kg}$ per minute IV result in dose-dependent accumulation of cyanide, and the risk of cyanide toxicity must be considered. Therefore, as other less toxic drugs are widely available, a reasonable approach might be to change to a different medication if the required dose approaches 2 $\mu\text{g}/\text{kg}$ per minute. Delivery of the SNP infusion as protected from light by aluminum foil is most often via an infusion pump.

Organ-Specific Effects

Cardiovascular

Baroreceptor-mediated reflex responses to SNP-induced decreases in systemic blood pressure manifest as tachycardia and increased myocardial contractility. These reflex-mediated responses may oppose the blood pressure-lowering effects of SNP. Although decreased venous return would tend to decrease cardiac output, the net effect is often an increase in cardiac output due to reflex-mediated increases in peripheral sympathetic nervous system activity combined with decreased impedance to left ventricular ejection. In the setting of left ventricular failure, SNP decreases systemic vascular resistance, pulmonary vascular resistance, and right atrial pressure, whereas the effect on cardiac output depends on the initial left ventricular end-diastolic pressure. There is no evidence that SNP exerts direct inotropic or chronotropic effects on the heart.

The SNP may increase the area of damage associated with a myocardial infarction through a phenomenon called “coronary steal.”⁷⁰ The SNP dilates resistance vessels in nonischemic myocardium, resulting in diversion of blood flow away from ischemic areas where collateral blood vessels are already maximally dilated. Decreases in diastolic blood pressure produced by SNP may also contribute to myocardial ischemia by decreasing coronary perfusion pressure and associated coronary blood flow.⁷¹

Renal

The SNP-induced decreases in systemic blood pressure may result in decreases in renal function. Release of renin may accompany blood pressure decreases produced by SNP and contribute to blood pressure overshoots when the drug is discontinued.⁷² Pretreatment with a competitive inhibitor of angiotensin II prevents blood pressure overshoots after discontinuation of SNP, thus confirming the participation of the renin-angiotensin system in this response.⁷³ Increased plasma concentrations of catecholamines also accompany hypotension produced by SNP.

Hepatic

In animals, SNP-induced decreases in systemic blood pressure do not result in hepatic hypoxia or changes in hepatic blood flow.⁷¹ Furthermore, hepatic blood flow does not change when cardiac output is maintained in anesthetized patients, despite 20% to 60% decreases in systemic blood pressure produced by SNP.⁷⁴

Cerebral

The SNP increases cerebral blood flow and cerebral blood volume. In patients with decreased intracranial compliance, this may increase intracranial pressure (greater than the increase produced by nitroglycerin). It is likely that the rapidity of systemic blood pressure decrease produced by SNP exceeds the capacity of the cerebral circulation to autoregulate its blood flow such that intracranial pressure and cerebral blood flow change simultaneously but in opposite directions.⁷⁵ Nevertheless, increases in intracranial pressure produced by SNP are maximal during modest decreases (<30%) in mean arterial pressure. When SNP-induced decreases in mean arterial pressure are greater than 30% of the awake level, the intracranial pressure decreases to below the awake level.⁷⁶ Furthermore, decreasing blood pressure slowly over 5 minutes with SNP in the presence of hypocapnia and hyperoxia negates the increase in intracranial pressure that accompanies the rapid infusion of nitroprusside.⁷⁷ Patients with known inadequate cerebral blood flow as associated with dangerously increased intracranial pressure or carotid artery stenosis should probably not be treated with SNP. During cardiopulmonary bypass, SNP has been shown to have no direct effect on cerebral vasculature and autoregulation is preserved.⁷⁸ The potential adverse effects of SNP on intracranial pressure are not present if the drug is administered after the dura has been surgically opened.

Pulmonary

Decreases in the partial pressure of arterial oxygen (PaO_2) may accompany the infusion of SNP and other peripheral vasodilators used to produce controlled hypotension. Attenuation of hypoxic pulmonary vasoconstriction by peripheral vasodilators is the presumed mechanism.⁵⁴ Addition of propranolol to the vasodilator regimen does not alter the magnitude of decrease in PaO_2 .⁷⁹ Furthermore, peripheral vasodilator-induced decreases in blood pressure are more likely to increase the shunt fraction in patients with normal lungs than in those with chronic obstructive pulmonary disease.⁸⁰ It is speculated that hypotension in normal

patients leads to decreased pulmonary artery pressure such that preferential perfusion of dependent but poorly ventilated alveoli occurs. In contrast, patients with chronic obstructive pulmonary disease may develop destructive vascular changes that prevent alterations in the distribution of pulmonary blood flow in response to vasodilation. The addition of positive end-expiratory pressure may reverse vasodilator-induced decreases in the PaO_2 .⁸¹

Hematologic

Increased intracellular concentrations of cGMP, as produced by SNP and nitroglycerin, have been shown to inhibit platelet aggregation.⁸² Infusion rates of SNP of greater than 3 $\mu\text{g}/\text{kg}$ per minute may result in decreases in platelet aggregation and increased bleeding time.⁸³ The postoperative stress-induced increase in platelet aggregation is absent in SNP-treated patients.⁸⁴ Increased bleeding time could also be the result of vasodilation secondary to a direct effect of SNP on vascular tone. However, clinical measures of intraoperative bleeding are not increased in SNP-treated patients, suggesting that decreased ability of platelets to aggregate during and after controlled hypotension does not have an adverse clinical effect.⁸⁴

Toxicity

Cyanide Toxicity

Clinical evidence of cyanide toxicity may occur when the rate of IV SNP infusion is greater than 2 $\mu\text{g}/\text{kg}$ per minute or when sulfur donors and methemoglobin are exhausted, thus allowing cyanide radicals to accumulate. Because any free cyanide radical may bind inactive tissue cytochrome oxidase and prevent oxidative phosphorylation, increased cyanide concentrations may precipitate tissue anoxia, anaerobic metabolism, and lactic acidosis. Children may be less able to mobilize thiosulfate stores despite increasing cyanide concentrations, leading to accelerated toxicity.

Regardless of the SNP infusion rate or total administered dose, cyanide toxicity should be suspected in any patient requiring an increasing dose especially more than 2 $\mu\text{g}/\text{kg}$ per minute or in a previously responsive patient who becomes less or unresponsive to the drug. Mixed venous partial pressure of oxygen (PvO_2) is increased in the presence of cyanide toxicity, indicating paralysis of cytochrome oxidase and inability of tissues to use oxygen. At the same time, metabolic acidosis (plasma lactate concentrations of >10 mM, which correlates with blood cyanide concentrations of >40 μM) develops as a reflection of anaerobic metabolism in the tissues. Decreased cerebral oxygen use is evidenced by the increased cerebral venous oxygen content. In awake patients, CNS dysfunction (mental status changes, seizures) may occur.

Treatment of Cyanide Toxicity. Appearance of tachyphylaxis in a previously sensitive patient in association with metabolic acidosis and increased mixed venous Po_2 mandates immediate discontinuation of SNP and administration of 100% oxygen despite normal oxygen saturation. Sodium bicarbonate is administered to correct metabolic acidosis. Sodium thiosulfate, 150 mg/kg IV administered over 15 minutes, has historically been the recommended first-line treatment for cyanide toxicity.⁶⁶ Thiosulfate acts as a sulfur donor to convert cyanide to thiocyanate, which is generally nontoxic (see following discussion). However, due to good side effect profile and increased availability, hydroxocobalamin has joined thiosulfate as part of the first-line treatment for cyanide toxicity, with both drugs frequently being used in conjunction.^{85,86} Hydroxocobalamin (vitamin B_{12a}), which binds cyanide to form cyanocobalamin (vitamin B₁₂), is administered as a 5-g initial dose, with the option for a second dose depending on clinical response.⁸⁷ In addition to being expensive, hydroxocobalamin may produce a reddish discoloration of the skin and mucous membranes. It may interfere with co-oximetry blood gas analysis, which is a relevant problem when coadministering drugs that are known to cause methemoglobinemia (ie, nitrates).⁸⁸ If cyanide toxicity is severe, with deteriorating hemodynamics and metabolic acidosis, the recommended treatment is slow IV administration of sodium nitrate, 5 mg/kg. Sodium nitrate converts hemoglobin to methemoglobin, which acts as an antidote by converting cyanide to cyanomethemoglobin.

Thiocyanate Toxicity

Thiocyanate is cleared slowly by the kidneys, with an elimination half-time of 3 to 7 days.⁶⁶ Clinical thiocyanate toxicity is rare, as thiocyanate is 100-fold less toxic than cyanide. In patients with normal renal function, 7 to 14 days of SNP infusion in the 2 to 5 µg/kg per minute range may be required to produce potentially toxic thiocyanate blood concentrations. The SNP infusions for 3 to 6 days may result in thiocyanate toxicity in patients with chronic renal failure who are not undergoing periodic hemodialysis.

Nonspecific symptoms of thiocyanate toxicity include fatigue, tinnitus, nausea, and vomiting. Clinical evidence of neurotoxicity produced by thiocyanate includes hyperreflexia, confusion, psychosis, and miosis. Toxicity may progress to seizures and coma. Increased thiocyanate concentrations competitively inhibit uptake and binding of iodine in the thyroid gland, sometimes producing clinical hypothyroidism. Thiocyanate clearance can be facilitated by dialysis. Oxyhemoglobin can slowly oxidize thiocyanate back to sulfate and cyanide, but this is insufficient to cause cyanide toxicity.

Methemoglobinemia

Adverse effects from methemoglobinemia produced by SNP breakdown are unlikely even in patients with a congenital inability to convert methemoglobin to hemoglobin (methemoglobin reductase deficiency).⁶⁶ The total SNP dose required to produce 10% methemoglobinemia exceeds 10 mg/kg. Patients receiving such high doses of SNP who present with evidence of impaired oxygenation despite an adequate cardiac output and arterial oxygenation should have methemoglobinemia included in the differential diagnosis. Measurement of methemoglobin via co-oximetry may be helpful in these patients.

Clinical Use

The use of SNP, as mentioned earlier, has significantly declined with the introduction of more selective arterial agents, which have a greater margin of safety and much less or absent toxicity. In addition, selective arterial agents do not generally have such a dramatic or acute effect on blood pressure due to preservation of venous tone. Before the availability of these drugs, SNP was used widely and well studied in the settings of controlled hypotension, hypertensive emergencies, aortic and cardiac surgery, and heart failure. In this latter population, the combined preload and afterload effect is still a possible advantage but at the cost of blood pressure lability and systemic toxicity. It is likely the use of SNP will continue to decline as experience grows with the newer agents.

Nitrates

Nitroglycerin is an organic nitrate that acts principally on venous capacitance vessels and large coronary arteries to produce peripheral pooling of blood and decreased cardiac ventricular wall tension.^{89,90} However, as the dose of nitroglycerin is increased, there is also relaxation of arterial vascular smooth muscle. Nitroglycerin can produce pulmonary vasodilation equivalent to the degree of systemic arterial vasodilation. The most common clinical use of nitroglycerin is sublingual or IV administration for the treatment of angina pectoris as a result of either atherosclerosis of the coronary arteries or intermittent vasospasm of these vessels. Controlled hypotension can also be achieved with the continuous infusion of nitroglycerin.

Mechanism of Action

Nitroglycerin, like SNP, generates NO, which stimulates production of cGMP to cause peripheral vasodilation (see earlier discussion). In contrast to SNP, which spontaneously produces NO, nitroglycerin requires the presence of thio-containing compounds. In this regard, the nitrate group of nitroglycerin is biotransformed to NO through a glutathione-dependent pathway involving both glutathione and glutathione S-transferase. Nitroglycerin is not recommended in patients with hypertrophic obstructive cardiomyopathy or in the presence of severe aortic stenosis, where venous pooling may lead to syncope.

Route of Administration

Nitroglycerin is most frequently administered by the sublingual route, but it is also available as an oral tablet, a buccal or transmucosal tablet, a sublingual spray, a transdermal ointment, or a continuous IV infusion. Sublingual administration of nitroglycerin results in peak plasma concentrations within 4 minutes. Only about

15% of the blood flow from the sublingual area passes through the liver, which limits the initial first-pass hepatic metabolism of nitroglycerin. In contrast, nitroglycerin is well absorbed after oral administration, but it is largely inactive because of first-pass hepatic metabolism.

Transdermal absorption of nitroglycerin, 5 to 10 mg over 24 hours, provides sustained protection against myocardial ischemia. The plasma concentration resulting from transdermal absorption of nitroglycerin is low, but tolerance to the drug effect occurs when the patches are left in place for longer than 24 hours. It is possible that removing the patches after 14 to 16 hours will prevent the development of tolerance.

Continuous infusion of nitroglycerin, via special delivery tubing to decrease absorption of the drug into plastic, is a useful approach to maintain a constant delivered concentration of nitroglycerin.

Pharmacokinetics

Nitroglycerin has an elimination half-time of about 1.5 minutes.⁹⁰ There is a large volume of distribution, reflecting tissue uptake, and it has been estimated that only 1% of total body nitroglycerin is present in the plasma. For this reason, plasma nitroglycerin concentrations may vary widely because of differences in tissue binding.

Methemoglobinemia

The nitrite metabolite of nitroglycerin is capable of oxidizing the ferrous ion in hemoglobin to the ferric state with the production of methemoglobin.^{91,92} In particular, high doses of nitroglycerin may produce methemoglobinemia in patients with hepatic dysfunction. Treatment of methemoglobinemia is as discussed earlier with SNP toxicity.

Tolerance

A limitation to the use of all nitrates is the development of tolerance to their vasodilating effects. Tolerance is dose dependent and duration dependent, usually manifesting within 24 hours of sustained treatment. If ischemia occurs during continuous administration of nitroglycerin, responsiveness to the anti-ischemic effects of the nitrate can usually be restored by increasing the dose. The mechanism of tolerance is not well understood but may reflect a change in the vasculature that limits the vasodilating effects of the nitrates. A drug-free interval of 12 to 14 hours is recommended to reverse tolerance to nitroglycerin and other nitrates. Rebound myocardial ischemia may occur during the drug-free interval.

Clinical Use

Perioperatively, nitroglycerin in all its forms is used to treat suspected myocardial ischemia as well as volume overload in the setting of heart failure (preload reduction). As a systemic antihypertensive, both for treatment and achieving controlled hypotension, nitroglycerin infusion can be effective, but its preferential effect on veins rather than arteries can make it less effective in severe hypertension than drugs, which preferentially act on the arteries. Although nitroglycerin has no “toxicity” (other than possible methemoglobinemia with high doses), its use for hypertension has declined with the availability of IV nicardipine and fenoldopam.

Isosorbide Dinitrate

Isosorbide dinitrate is a commonly administered oral nitrate for the prophylaxis of angina pectoris and for preload reduction in patients with heart failure. Its effects are very similar to that of nitroglycerin, but as an oral agent, isosorbide dinitrate is well absorbed from the gastrointestinal tract, and it is not subject to the extensive first-pass metabolism that limits oral use of nitroglycerin. It exerts a physiologic effect lasting up to 6 hours when taken in doses of 60 to 120 mg. The longer acting sustained release form provides a prolonged antianginal effect and improves exercise tolerance for up to 6 hours. Isosorbide dinitrate may also be administered sublingually, producing an effect lasting up to 2 hours. The metabolite of isosorbide dinitrate, isosorbide-5-mononitrate, is more active than the parent compound. Orthostatic hypotension accompanies acute administration of isosorbide dinitrate, but tolerance to this and other pharmacologic effects seems to develop with chronic therapy.

Hydralazine

Hydralazine is a direct systemic arterial vasodilator, which both hyperpolarizes smooth muscle cells and activates guanylate cyclase to produce vasorelaxation.⁹³ Arterial vasodilation by hydralazine produces reflex sympathetic nervous system stimulation with resulting increases in heart rate and myocardial contractility, so this drug is not generally recommended for patients with myocardial ischemia or coronary disease. It is an effective afterload-reducing agent and is still used in combination with nitrates for outpatient treatment of congestive heart failure and for intermittent IV dosing in the perioperative period or critical care setting. Although it has been widely used in hypertensive disorders associated with pregnancy, other agents may be associated with less adverse outcomes.⁹⁴ Long-term hydralazine use is limited due to an association with a systemic autoimmune syndrome that has features of drug-induced lupus and antineutrophil cytoplasmic antibody-associated vasculitis.⁹⁵ Acute IV administration has a slightly delayed onset, making it less appealing than other immediate-onset medications.

Fenoldopam

Fenoldopam is a dopamine type 1 receptor agonist, causing systemic arterial dilation through increasing cAMP. It has a particular action of increasing renal blood flow and increasing urine output and also increasing splanchnic blood flow due to the density of dopamine type 1 receptors in these beds.⁹⁶ Because of this action, it has been viewed by some as a possible “new renal dopamine,” which might have a renal protective effect, but evidence to support this hypothesis is weak. There is no question, however, that when compared to other IV antihypertensive drugs such as SNP or nicardipine, there is greater urine output with fenoldopam for the same degree of antihypertensive action. Fenoldopam is only available in an IV preparation, it has a rapid onset and 10-minute elimination half-life. As is the case with other arterial dilators, there is a baroreflex-mediated increase in heart rate and plasma catecholamine level associated with its use. Adverse effects are limited to an increase in intraocular pressure, making this drug unsuitable for patients with glaucoma.

Diuretics

As discussed earlier, diuretics continue to be first-line oral agents used for essential hypertension. Patients are most likely to be prescribed a thiazide drug, with more potent loop diuretics (furosemide, bumetanide) reserved for patients where thiazides are less effective such as patients with renal insufficiency or heart failure. Diuretics are not, strictly speaking, vasodilators, although there is evidence for a venodilating effect of IV furosemide.⁹⁷ Both thiazide and loop diuretics cause potassium loss, and their use generally mandates supplementation with potassium and often magnesium. This is true both for oral outpatient use and acute IV dosing in the perioperative or critical care setting.

Aldosterone antagonists or “potassium-sparing” agents are less potent than loop diuretics but have a clear role in patients with heart failure where their addition to other antihypertensive drugs (eg, ACE inhibitors) confers a survival benefit. This is possibly due to blocking aldosterone effects on the heart.

Drugs Not Discussed

The earlier discussion of antihypertensive drugs and vasodilators has not included a number of older agents, which are rarely used now for this indication in clinical practice in North America. These include trimethaphan, diazoxide, alpha-methyldopa, and adenosine. The reader is referred to old texts for a discussion of these agents.

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Antiarrhythmic Drugs*

Updated by: Wendy Smith • James Ramsay

Cardiac arrhythmias occur commonly in the perioperative period, most of which are relatively benign and are due to transient changes in physiology, surgical stimuli, or the effect of anesthetic agents. Arrhythmias that require treatment are most commonly supraventricular, with atrial fibrillation being especially common after cardiac surgery.^{1,2} The chronic use of antiarrhythmic drugs for the treatment and prevention of cardiac arrhythmias is limited by the potential for these drugs to depress left ventricular contractility and the triggering of new arrhythmias (see the “[Proarrhythmic Effects](#)” section).³ For this reason, alternatives to pharmacologic therapy have been sought. Improved survival for those receiving implantable cardiac defibrillator devices compared with antiarrhythmic drugs has altered the treatment paradigms for patients with ventricular arrhythmias, although pharmacologic therapy remains first line in the case of structural heart disease.^{4,5} Similarly, catheter ablation techniques are preferred treatments for many supraventricular arrhythmias including atrial flutter and certain types of atrial fibrillation. As a result, pharmacologic treatment of cardiac arrhythmias is principally used to suppress atrial fibrillation and atrial flutter that is not responsive to catheter ablation treatment and for patients with implantable cardioverter-defibrillator devices who are receiving frequent indicated electrical shocks.

Pharmacologic treatment of cardiac arrhythmias and disturbances of the conduction of cardiac impulses with antiarrhythmic drugs is based on an understanding of the electrophysiologic basis of the abnormality and the mechanism of action of the therapeutic drug to be administered.^{1,6} The two major physiologic mechanisms that cause ectopic cardiac arrhythmias are reentry and enhanced automaticity. Factors encountered in the perioperative period that facilitate cardiac arrhythmias due to both mechanisms include hypoxemia, electrolyte and acid–base abnormalities, myocardial ischemia, altered sympathetic nervous system activity, bradycardia, and the administration of certain drugs. It is not commonly appreciated that alkalosis is even more likely than acidosis to trigger cardiac arrhythmias. Hypokalemia and hypomagnesemia predispose to ventricular arrhythmias and must be suspected in patients who are being treated with diuretics. Increased sympathetic nervous system activity, as may be encountered during laryngoscopy or surgical stimulation, lowers the threshold for ventricular fibrillation, a phenomenon that is attenuated by β blockade and vagal stimulation.⁷ Bradycardia predisposes to ventricular arrhythmias by causing a temporal dispersion of refractory periods among Purkinje fibers, creating an electrical gradient between adjacent cells. Enlargement of a failing left ventricle stretches individual myocardial cells and can thereby induce cardiac arrhythmias. Decreasing left ventricular volume with administration of digitalis, diuretics, or vasodilators helps to control cardiac arrhythmias that are precipitated by this mechanism.

In some patients, correction of identifiable precipitating events is not sufficient to suppress cardiac ectopic rhythms, and therefore, specific cardiac antiarrhythmic drugs may be indicated. Drugs administered for the chronic suppression of cardiac arrhythmias pose little threat to the uneventful course of anesthesia and should be continued up to the time of induction of anesthesia.^{1,8} As mentioned earlier, the majority of cardiac arrhythmias that occur during anesthesia do not require therapy. Cardiac arrhythmias, however, do require treatment when hemodynamic function is compromised or the disturbance predisposes to more serious cardiac arrhythmias.

General anesthetic-related cardiac arrhythmias have been ascribed to abnormal pacemaker activity characterized by suppression of the sinoatrial node, with the emergence of latent pacemakers within or below the atrioventricular tissues.⁶ Furthermore, development of reentry circuits is likely to be important in the mechanism of cardiac arrhythmias that occur during anesthesia. Certain anesthetics, particularly volatile drugs, may have effects on the specialized conduction system for cardiac impulses.

Mechanism of Action

It is well established that antiarrhythmic drugs produce pharmacologic effects by blocking passage of ions across sodium, potassium, and calcium ion channels present in the heart ([Figure 21.1](#)). The cardiac action potential results from the interplay of multiple inward and outward currents via specific ion channels responsible for each of the five phases. The duration of each phase of the action potential differs in atrial compared with ventricular myocardium and the specialized systems for conduction of cardiac impulses differ in ion channel density. Ion channels are large membrane-bound glycoproteins that provide a pathway across cell membranes for the passage of ions. Ion channels exist in different states (open, inactivated, closed). In the inactivated state, the ion channel is unresponsive to a continued or new stimulus. The resting state is more prevalent during diastole, the active state occurs during the upstroke of the action potential, and the inactivated state occurs during the plateau phase of repolarization.

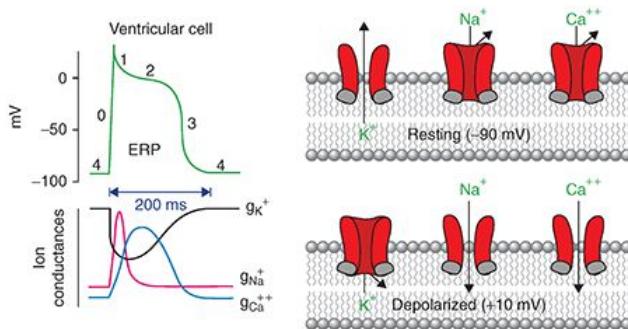


FIGURE 21.1 The physiologic basis of the cardiac action potential. Phase 0 represents rapid depolarization as a result of opening of Na^+ channels and closing of K^+ channels. Phase 1 is the period of initial repolarization that results from closure of Na^+ and opening of K^+ channels. Phase 2 is the plateau phase that results from the sustained Ca^{++} current that began with the initial depolarization. Phase 3 is repolarization due to opening of K^+ and closure of Ca^{++} channels. Phase 4 is the resting potential during which K^+ channels are open and Na^+ and Ca^{++} channels are closed. The effective refractory period (ERP) is the time during which the cell cannot be depolarized again. Redrawn based on Klabunde RE, ed. Cardiovascular Physiology Concepts. 2nd ed. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2011.

The effects of cardiac antiarrhythmic drugs on the action potential and effective refractory period of the cardiac action potential determine the clinical effect of these drugs. Drugs that primarily block inward sodium ion flow will slow conduction and result in suppression of the maximum upstroke velocity of the cardiac action potential. Potassium channel blocking drugs prolong repolarization by increasing the duration of the cardiac action potential and the effective refractory period resulting in prolongation of the QTc interval on the electrocardiogram (ECG). Calcium channels are present in myocardial cells, and the α subunit of L and T calcium ion channels is the site of action of some cardiac antiarrhythmic drugs.

Classification

Our knowledge of cardiac ion channels and the actions of antiarrhythmic drugs has greatly increased since the development of the original Vaughn-Williams classification ([Table 21.1](#)). One of the benefits and drawbacks of Vaughn-Williams is that it is simple and easy to understand; however, this simplicity prevents a thorough representation of the multifaceted effects of each drug. Alternate classification systems have been proposed, but a new gold standard has not yet been widely accepted. However, as our understanding and treatment of arrhythmias becomes more nuanced, there will likely be modifications to the original classification and the options bear mentioning. One of the first attempts is known as the **Sicilian Gambit** of 1991 in which the physiologic basis of the arrhythmia, rather than the predominant pharmacologic action of a drug, was the primary descriptor of each class.⁹ More recently, a proposal for a revision of Vaughn-Williams has been put forward.¹⁰ This updated system describes the existing classes with more granularity and has added several new classes for a more inclusive picture of the complex physiologic actions of antiarrhythmic

targets. For the purposes of this text, Vaughn-Williams continues to serve as an excellent scaffolding on which an anesthesiologist can build an introductory knowledge of antiarrhythmic drugs as long as the limitations of the system are acknowledged.

TABLE 21.1

Classification of cardiac antiarrhythmic drugs

Class I (inhibit fast sodium ion channels)
Class IA
Quinidine
Procainamide
Disopyramide
Moricizine
Class IB
Lidocaine
Tocainide
Mexiletine
Class IC
Flecainide
Propafenone
Class II (decrease rate of depolarization)
Esmolol
Propranolol
Acebutolol
Class III (inhibit potassium ion channels)
Amiodarone
Dronedarone
Sotalol
Ibutilide
Dofetilide
Class IV (inhibit slow calcium channels)
Verapamil
Diltiazem

According to the Vaughn-Williams classification, cardiac arrhythmic drugs are most commonly placed into four groups based primarily on the ability of the drug to control arrhythmias by blocking specific ion channels and currents during the cardiac action potential ([Tables 21.1](#) and [21.2](#)).^{11,12} Few cardiac antiarrhythmic drugs demonstrate completely specific effects on cardiac ion channels. It should be noted that other characteristics including the impact of the drug on autonomic nervous system activity and myocardial contractility may be more important clinically and should be taken into consideration when choosing a specific agent. Antiarrhythmic drugs also differ in their pharmacokinetics and efficacy in treating specific types of arrhythmias ([Tables 21.3](#) and [21.4](#)).⁸

TABLE 21.2

Electrophysiologic and electrocardiographic effects of cardiac antiarrhythmic drugs

	Class IA	Class IB	Class IC	Class II	Class III	Class IV
Depolarization rate (phase 0)	Decreased	No effect	Greatly decreased	No effect	No effect	No effect
Conduction velocity	Decreased	No effect	Greatly decreased	Decreased	Decreased	No effect
Effective refractory	Greatly	Decreased	Increased	Decreased	Greatly	No effect

period	increased				increased	
Action potential duration	Increased	Decreased	Increased	Increased	Greatly increased	Decreased
Automaticity	Decreased	Decreased	Decreased	Decreased	Decreased	No effect
P-R duration	No effect	No effect	Increased	No effect or increased	Increased	No effect or increased
QRS duration	Increased	No effect	Greatly increased	No effect	Increased	No effect
QTc duration	Greatly increased	No effect or decreased	Increased	Decreased	Greatly increased	No effect

TABLE 21.3

Pharmacokinetics of common cardiac antiarrhythmic drugs

	Principal clearance mechanism	Protein binding (%)	Elimination half-time* (hours)	Therapeutic plasma concentration
Quinidine	Hepatic	80-90	5-12	1.2-4.0 µg/mL
Procainamide	Renal/hepatic	15	2.5-5.0	4-8 µg/mL
Disopyramide	Renal/hepatic	15	8-12	2-4 µg/mL
Lidocaine	Hepatic	55	1.4-8.0	1-5 µg/mL
Tocainide	Hepatic/renal	10-30	12-15	4-10 µg/mL
Mexiletine	Hepatic	60-75	6-12	0.75-2.00 µg/mL
Flecainide	Hepatic	30-45	13-30	0.3-1.5 µg/mL
Propafenone	Hepatic	>95	5-8	
Propranolol	Hepatic	90-95	2-4	10-30 ng/mL
Amiodarone	Hepatic	96	8-107 d	1.5-2.0 µg/mL
Dronedarone	Hepatic	98	13-19	
Sotalol	Renal	0	10-20	
Verapamil	Hepatic	90	4.5-12.0	100-300 ng/mL

*Half-times are for patients with normal renal and hepatic function.

TABLE 21.4

Efficacy of cardiac antiarrhythmic drugs

	Conversion of atrial fibrillation	Paroxysmal supraventricular tachycardia	Premature ventricular contractions	Ventricular tachycardia
Quinidine	+	++	++	+
Procainamide	+	++	++	++
Disopyramide	+	++	++	++
Lidocaine	+	0	++	++
Tocainide	0	0	++	++
Mexiletine	0	0	++	++
Moricizine	0	0	++	++
Flecainide	0	+	++	++
Propafenone	0	+	++	++
Propranolol	+	++	+	+
Amiodarone	+	++	++	++

Sotalol	++	+	+	+
Verapamil	+	++	0	0
Diltiazem	+	++	0	0
Digitalis	++	++	0	0
Adenosine	0	++	0	0

Abbreviations: 0, no effect; +, effective; ++, highly effective.

Class I Drugs

Class I drugs inhibit fast sodium channels during depolarization (phase 0) of the cardiac action potential with resultant decreases in depolarization rate and conduction velocity (see [Figure 21.1](#)).¹¹

Class IA Drugs

Class IA drugs (quinidine, procainamide, disopyramide, moricizine) lengthen both the action potential duration and the effective refractory period reflecting sodium channel inhibition and prolonged repolarization owing to potassium channel blockade.

Class IB Drugs

Class IB drugs (lidocaine, mexiletine, tocainide, phenytoin) are less powerful sodium channel blockers and, unlike class IA drugs, shorten the action potential duration and refractory period in normal cardiac ventricular muscle. In ischemic tissue, lidocaine may also block adenosine triphosphate-dependent channels, thus preventing ischemia-mediated shortening of ventricular depolarization.

Class IC Drugs

Class IC drugs (flecainide, propafenone) are potent sodium channel blockers and markedly decrease the rate of phase 0 depolarization and speed of conduction of cardiac impulses. These drugs have little effect on the duration of the cardiac action potential and the effective refractory period in ventricular myocardial cells but do shorten the duration of the action potential in Purkinje fibers. This inhomogeneity of effects on the rate of cardiac depolarization plus the slowing of cardiac conduction may contribute to the proarrhythmic effects of these drugs.

Class II Drugs

Class II drugs are primarily β -adrenergic antagonists. β -Adrenergic antagonists decrease the rate of spontaneous phase 4 depolarization resulting in decreased autonomic nervous system activity, which may be important in suppression of ventricular arrhythmia during myocardial ischemia and reperfusion. Drug-induced slowing of heart rate with resulting decreases in myocardial oxygen requirements is desirable in patients with coronary artery disease. β -Adrenergic antagonists slow the speed of conduction of cardiac impulses through atrial tissues resulting in prolongation of the P-R interval on the ECG, whereas the duration of action of the cardiac action potential in ventricular myocardium is not altered. These drugs are effective in decreasing the incidence of arrhythmia-related morbidity and mortality although the exact mechanism for this beneficial effect remains unclear.

Class III Drugs

Class III drugs (amiodarone, dronedarone, sotalol) primarily block potassium ion channels resulting in prolongation of cardiac depolarization, action potential duration, and the effective refractory period. These effects are beneficial in preventing cardiac arrhythmias by decreasing the proportion of the cardiac cycle during which myocardial cells are excitable and thus susceptible to a triggering event. Reentrant tachycardias may be suppressed if the action potential duration becomes longer than the cycle length of the tachycardia circuit.

In addition to class III effects, amiodarone exhibits sodium channel blockade (class I), β blockade (class II), and calcium channel blockade (class IV). Although this drug is US Food and Drug Administration (FDA)

approved for the treatment of refractory ventricular arrhythmias, it has become a widely used drug for the acute treatment and prevention of supraventricular and ventricular arrhythmias both in the operating room and the intensive care unit (see the following text).

Sotalol is a long-acting, noncardioselective β -blocking drug consisting of a racemic mixture of levorotatory and dextrorotatory isomers that possess similar class III effects. The levorotatory isomer of sotalol acts as a β -adrenergic antagonist, whereas the dextrorotatory isomer may increase mortality in patients with ventricular dysfunction and recent myocardial infarction. The reduced incidence of proarrhythmia effects seen with amiodarone or racemic sotalol treatment may be related to beneficial class II effects.

Another class III drug less commonly used is dofetilide, most likely to be prescribed by electrophysiologists in patients refractory to, or with side effects from other agents, but with a measurable incidence of proarrhythmia.

Class IV Drugs

Class IV drugs are the calcium blockers verapamil and diltiazem, which primarily act by inhibiting inward slow calcium ion currents that may contribute to the development of tachycardias. As such, these drugs may be useful in the treatment of both supraventricular tachyarrhythmias and idiopathic ventricular tachycardia. The dihydropyridine calcium blockers (nifedipine, nicardipine, nimodipine) do not have antiarrhythmic action.

Class 0 Drugs

As mentioned earlier, there are modern antiarrhythmic drug classifications, which recognize an expanded set of primary receptor targets.¹⁰ Although some new categories are theoretical, without corresponding pharmacologic agents, there is one “class 0” drug, which gained FDA approval in 2015 and is therefore worth discussing. Ivabradine is a novel drug that selectively inhibits the current in the sinoatrial node responsible for spontaneous slow depolarization and hence the heart rate. This has been termed the “funny current.” Ivabradine slows the heart rate, with greater effectiveness at higher heart rates.¹³ It has no hemodynamic effects other than on the heart rate and has been evaluated in clinical trials in patients with heart failure (normal and reduced ejection fraction) and coronary disease with heart failure, showing clinical benefit mostly in patients with heart failure and reduced ejection fraction with sinus rhythm >70 beats per minute and who are either on maximal doses of β blockers or are unable to take β blockers (the 2015 FDA-approved indication). The drug is only available in an oral formulation and is therefore unlikely to have utility in the acute perioperative setting; however, patients with heart failure may come to the operating room on this medication. Additionally, there is interest in its use as an isolated bradycardic agent in other settings such as the sinus tachycardia seen in sepsis.¹⁴

Proarrhythmic Effects

Proarrhythmia effects describe bradyarrhythmias or tachyarrhythmias that represent new cardiac arrhythmias associated with antiarrhythmic drug treatment.³ These include torsades de pointes (most common), incessant ventricular tachycardia, and wide complex ventricular rhythm.¹¹

Torsades de Pointes

Torsades de pointes is triggered by early afterdepolarizations in a setting of delayed repolarization and increased duration of refractoriness manifesting as prolongation of the QTc interval on the ECG. Class IA (quinidine and disopyramide) and class III drugs (amiodarone) prolong the QTc interval by potassium channel blockade providing the setting for torsades de pointes. Drug-induced torsades de pointes is often associated with bradycardia because the QTc interval is longer at slower heart rates. Exacerbating factors such as hypokalemia, hypomagnesemia, poor left ventricular function, and concomitant administration of other QT-prolonging drugs are important predisposing factors in the development of this life-threatening rhythm.

Incessant Ventricular Tachycardia

Incessant ventricular tachycardia may be precipitated by drugs that slow conduction of cardiac impulses (class IA and IC drugs) sufficiently to create a continuous ventricular tachycardia circuit (reentry). Incessant ventricular tachycardia is more likely to occur with high doses of class IC drugs and in patients with a prior history of sustained ventricular tachycardia and poor left ventricular function. Ventricular tachycardia due to this mechanism is generally slower because of the drug effect but may be resistant to drugs or electrical therapy. This rhythm is rarely associated with class IB drugs, which have a weaker blocking effect of sodium channels.

Wide Complex Ventricular Rhythm

Wide complex ventricular rhythm is usually associated with class IC drugs in the setting of structural heart disease. Excessive plasma concentrations of the drug or an abrupt change in the dose may result in this arrhythmia. Wide complex ventricular rhythm is thought to reflect a reentrant tachycardia and easily degenerates to ventricular fibrillation.

Efficacy and Results of Treatment With Cardiac Antiarrhythmic Drugs

Chronic suppression of ventricular ectopy with an antiarrhythmic drug other than amiodarone does not prevent future life-threatening arrhythmias and may increase mortality.¹¹ In fact, patients treated with class IC drugs experienced a higher incidence of sudden cardiac arrest reflecting the proarrhythmia effects of these drugs. Conversely, β-adrenergic antagonists that do not typically suppress ventricular arrhythmias appear to decrease mortality and the risk of life-threatening ventricular arrhythmias. In patients with a history of myocardial infarction and ventricular arrhythmias, mortality was increased in those who received class IA and IC drugs, whereas mortality was decreased with amiodarone and β-adrenergic antagonists.¹⁵ Survivors of cardiac arrest have a high risk of subsequent ventricular fibrillation and treatment of these patients with amiodarone results in fewer life-threatening cardiac events. The proarrhythmic and negative inotropic effects of class IA and IC drugs precludes their administration to patients with congestive heart failure. In these patients, administration of amiodarone appears to be safe and effective.

Prophylactic Antiarrhythmic Drug Therapy

Although commonly used in the past, lidocaine is no longer recommended as prophylactic treatment for patients in the early stages of acute myocardial infarction and without malignant ventricular ectopy.¹⁶ In fact, lidocaine does not decrease and may increase mortality because of an increase in the occurrence of fatal bradyarrhythmias and asystole.

Calcium channel antagonists are not recommended as routine treatment of patients with acute myocardial infarction because mortality is not decreased by these drugs. Calcium channel blockers may be administered to patients in whom myocardial ischemia persists despite treatment with aspirin, heparin, nitroglycerin, and β-adrenergic antagonists.

Magnesium is involved in many enzymatic reactions, produces systemic and coronary vasodilation, inhibits platelet aggregation, and decreases myocardial reperfusion injury. Data on the ability of magnesium to decrease mortality following myocardial infarction are conflicting.¹⁷ Treatment with magnesium is indicated in patients following an acute myocardial infarction who develop torsades de pointes ventricular tachycardia.¹⁸

In patients with heart failure, amiodarone reduces the risk of sudden cardiac death by 29% and therefore represents a viable alternative in patients who are not eligible for or who do not have access to implanted cardiac defibrillator therapy for the prevention of sudden cardiac death from arrhythmias.¹⁹ Amiodarone can be considered as an adjuvant therapy to implanted cardiac defibrillator in preventing recurrent shocks. However, amiodarone therapy is neutral with respect to all-cause mortality and is associated with a two- and fivefold increased risk of pulmonary and thyroid toxicity, respectively.¹⁹ Prophylactic dofetilide did not demonstrate a mortality benefit either.²⁰ In summary, there is little role for prophylactic antiarrhythmic medications for the primary prevention of sudden cardiac death in patients with heart failure with the exception of amiodarone.

Atrial fibrillation after heart surgery is a common complication that has been associated with prolonged hospitalization and cardiovascular morbidity. Prophylactic therapy with amiodarone, β blockers, sotalol, and magnesium has been effective in reducing the occurrence of atrial fibrillation, length of hospital stay, and cost of hospital treatment and may be effective in reducing the risk of stroke.²¹

Decision to Treat Cardiac Arrhythmias

Drug treatment of cardiac arrhythmias is not uniformly effective and frequently causes side effects (see the “[Proarrhythmic Effects](#)” section).^{1,22} The benefit of antiarrhythmic drugs is clearest when it results in the immediate termination of a sustained tachycardia. There is no doubt that the termination of ventricular tachycardia by lidocaine or supraventricular tachycardia by adenosine or verapamil is a true benefit of antiarrhythmic therapy. Furthermore, when given for a limited period, side effects are less likely. Conversely, it has been difficult to demonstrate that antiarrhythmic drugs alleviate symptoms related to chronic cardiac arrhythmias, a situation in which the risk of side effects is greater. The increase in long-term mortality associated with certain drugs (Cardiac Arrhythmia Suppression Trial and other trials) raises the possibility that some antiarrhythmics result in sensitization of the myocardium to concurrent triggering factors (myocardial ischemia, neurohumoral activation, myocardial stretch, slow healing process after a myocardial infarction) that then elicit cardiac arrhythmias.^{15,22} The mechanism by which β -adrenergic antagonists decrease mortality after an acute myocardial infarction is not known.

The value of monitoring plasma drug concentrations in minimizing the risks associated with therapy is not established. In fact, many side effects appear to depend as much on the nature and extent of the underlying heart disease as on increased plasma drug concentrations.²²

Antiarrhythmic Drug Pharmacology

Quinidine

Quinidine is a class IA drug that is effective in the treatment of acute and chronic supraventricular arrhythmias ([Figure 21.2](#)).²³ Due to its side effect profile and low therapeutic index (see the following text), and the availability of newer agents, quinidine is rarely used. It can prevent recurrence of supraventricular tachyarrhythmias or suppress premature ventricular contractions and can slow the ventricular rate in the presence of atrial fibrillation, and about 25% of patients with new-onset atrial fibrillation will convert to normal sinus rhythm when treated with quinidine. Supraventricular tachyarrhythmias associated with Wolff-Parkinson-White syndrome are effectively suppressed by quinidine.

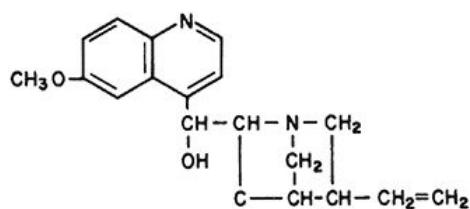


FIGURE 21.2 Quinidine.

Quinidine is most often administered orally in a dose of 200 to 400 mg four times daily. Oral absorption of quinidine is rapid, with peak concentrations in the plasma attained in 60 to 90 minutes and an elimination half-time of 5 to 12 hours. The therapeutic blood level of quinidine is 1.2 to 4.0 μ g/mL. Intravenous (IV) quinidine is rarely used due to vasodilation and myocardial depression.

Mechanism of Action

Quinidine is the dextroisomer of quinine and, like quinine, has antimalarial and antipyretic effects. Unlike quinine, however, quinidine has intense effects on the heart. For example, quinidine decreases the slope of phase 4 depolarization, which explains its effectiveness in suppressing cardiac arrhythmias caused by enhanced automaticity. Quinidine increases the fibrillation threshold in the atria and ventricles. Quinidine-

induced slowing of the conduction of cardiac impulses through normal and abnormal fibers may be responsible for the ability of quinidine to occasionally convert atrial flutter or fibrillation to normal sinus rhythm. This drug can abolish reentry arrhythmias by prolonging conduction of cardiac impulses in an area of injury, thus converting one-way conduction blockade to two-way conduction blockade. A decrease in the atrial rate during atrial flutter or fibrillation may reflect slowed conduction velocity, a prolonged effective refractory period in the atria, or both.

Metabolism and Excretion

Quinidine is hydroxylated in the liver to inactive metabolites, which are excreted in the urine. About 20% of quinidine is excreted unchanged in the urine. Enzyme induction significantly shortens the duration of action of quinidine. The concurrent administration of phenytoin, phenobarbital, or rifampin may lower blood levels of quinidine by enhancing liver clearance. Because of its dependence on renal excretion and hepatic metabolism for clearance from the body, accumulation of quinidine or its metabolites may occur in the presence of impaired function of these organs. About 80% to 90% of quinidine in plasma is bound to albumin. Quinidine accumulates rapidly in most tissues except the brain.

Side Effects

Quinidine has a low therapeutic ratio, with heart block, hypotension, and proarrhythmia being potential adverse side effects. As the plasma concentration increases to more than 2 $\mu\text{g}/\text{mL}$, the P-R interval, QRS complex, and QTc interval on the ECG are prolonged. Patients with preexisting prolongation of the QTc interval or evidence of atrioventricular heart block on the ECG should not be treated with quinidine.

Patients in normal sinus rhythm treated with quinidine may show an increase in heart rate that is a result of presumably either an anticholinergic action and/or a reflex increase in sympathetic nervous system activity. This atropine-like action of quinidine opposes its direct depressant actions on the sinoatrial and atrioventricular nodes and is why digitalis is often given before quinidine therapy is initiated.

Allergic reactions may include drug rash or a drug fever that is occasionally associated with leukocytosis. Thrombocytopenia is a rare occurrence that is caused by drug-platelet complexes that evoke production of antibodies. Discontinuation of quinidine results in return of the platelet count to normal in 2 to 7 days. Nausea, vomiting, and diarrhea occur in about one-third of treated patients.

Like other cinchona alkaloids and salicylates, quinidine can cause cinchonism. Symptoms of cinchonism include tinnitus, decreased hearing acuity, blurring of vision, and gastrointestinal upset. In severe cases, there may be abdominal pain and mental confusion.

Because quinidine is an α -adrenergic blocking drug, it can interact in an additive manner with drugs that cause vasodilation. Quinidine also interferes with normal neuromuscular transmission and may accentuate the effect of neuromuscular blocking drugs. Recurrence of skeletal muscle paralysis in the immediate postoperative period has been observed in association with the administration of quinidine.²⁴

Procainamide

Procainamide is as effective as quinidine for the treatment of ventricular tachyarrhythmias but less effective in abolishing atrial tachyarrhythmias ([Figure 21.3](#)). Premature ventricular contractions and paroxysmal ventricular tachycardia are suppressed in most patients within a few minutes after IV administration, which is better tolerated than IV quinidine but may still cause hypotension. Procainamide can be administered IV at a rate not exceeding 100 mg every 5 minutes until the rhythm is controlled (maximum 15 mg/kg). When the cardiac arrhythmia is controlled, a constant rate of infusion (2-6 mg per minute) is used to maintain a therapeutic concentration of procainamide. The systemic blood pressure and ECG (QRS complex) are monitored continuously during infusion of this drug. The therapeutic blood level of procainamide is 4 to 8 $\mu\text{g}/\text{mL}$.

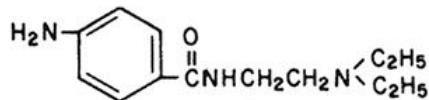


FIGURE 21.3 Procainamide.

Mechanism of Action

Procainamide is an analogue of the local anesthetic procaine. Procainamide possesses an electrophysiologic action similar to that of quinidine but produces less prolongation of the QTc interval on the ECG. As a result, paradoxical ventricular tachycardia is a rare feature of procainamide therapy. Procainamide has no vagolytic effect and can be used in patients with atrial fibrillation to suppress ventricular irritability without increasing the ventricular rate. Like quinidine, procainamide may prolong the QRS complex and cause ST-T wave changes on the ECG.

Metabolism and Excretion

Procainamide is eliminated by renal excretion and hepatic metabolism. In humans, 40% to 60% of procainamide is excreted unchanged by the kidneys. The dose of procainamide must be decreased when renal function is abnormal. In the liver, procainamide that has not been excreted unchanged by the kidneys is acetylated to *N*-acetyl procainamide (NAPA), which is also eliminated by the kidneys. This metabolite is cardioactive and probably contributes to the antiarrhythmic effects of procainamide. In the presence of renal failure, plasma concentrations of NAPA may reach dangerous levels. Eventually, 90% of an administered dose of procainamide is recovered as unchanged drug or its metabolites.

The activity of the *N*-acetyltransferase enzyme response for the acetylation of procainamide is genetically determined. In patients who are rapid acetylators, the elimination half-time of procainamide is 2.5 hours compared with 5 hours in slow acetylators. The blood level of NAPA exceeds that of procainamide in rapid but not slow acetylators. Unlike its analogue, procaine, procainamide is highly resistant to hydrolysis by plasma cholinesterase. Evidence of this resistance is the fact that only 2% to 10% of an administered dose of procainamide is recovered unchanged in the urine as para-aminobenzoic acid.

Only about 15% of procainamide is bound to plasma proteins. Despite this limited binding in plasma, procainamide is avidly bound to tissue proteins with the exception of the brain.

Side Effects

Similar to quinidine, use of procainamide has dramatically decreased due to its side effect profile and availability of newer agents. Hypotension that results from procainamide is more likely to be caused by direct myocardial depression than peripheral vasodilation. Indeed, rapid IV injection of procainamide is associated with hypotension, whereas higher plasma concentrations slow conduction of cardiac impulses through the atrioventricular node and intraventricular conduction system. Ventricular asystole or fibrillation may occur when procainamide is administered in the presence of heart block, as associated with digitalis toxicity. Direct myocardial depression that occurs at high plasma concentrations of procainamide is exaggerated by hyperkalemia. As with quinidine, ventricular arrhythmias may accompany excessive plasma concentrations of procainamide.

Chronic administration of procainamide may be associated with a syndrome that resembles systemic lupus erythematosus. Serositis, arthritis, pleurisy, or pericarditis may develop, but unlike systemic lupus erythematosus, vasculitis is not usually present. Patients with this lupus-like syndrome often develop antinuclear antibodies (positive antinuclear antibody test). Slow acetylators are more likely than rapid acetylators to develop antinuclear antibodies. Symptoms disappear when procainamide is discontinued.

As with many drugs, procainamide may cause drug fever or an allergic rash. Although agranulocytosis is rare, leukopenia and thrombocytopenia may be seen after chronic use of procainamide, often in association with the lupus-like syndrome. The most common early, noncardiac complications of procainamide are gastrointestinal disturbances, including nausea and vomiting.

Disopyramide

Disopyramide is comparable to quinidine in effectively suppressing atrial and ventricular tachyarrhythmias (**Figure 21.4**). Absorption of oral disopyramide is almost complete, resulting in peak blood levels within 2

hours of administration. Therapeutic plasma concentrations of disopyramide are 2 to 4 $\mu\text{g}/\text{mL}$. About 50% of the drug is excreted unchanged by the kidneys. As a result, the typical elimination half-time of 8 to 12 hours is prolonged in the presence of renal dysfunction. A dealkylated metabolite with less antiarrhythmic and atropine-like activity than the parent drug accounts for about 20% of the drug's elimination. Disopyramide is not available in an IV formulation.

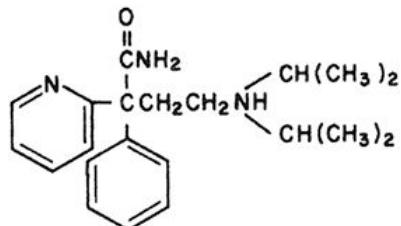


FIGURE 21.4 Disopyramide.

Side Effects

The most common side effects of disopyramide are dry mouth and urinary hesitancy, both of which are caused by the drug's anticholinergic activity. Some patients taking disopyramide also experience blurred vision or nausea. Prolongation of the QTc interval on the ECG and paradoxical ventricular tachycardia (similar to quinidine) may occur. For this reason, disopyramide should be administered cautiously if patients have known cardiac conduction effects. Disopyramide has significant myocardial depressant effects and can precipitate congestive heart failure and hypotension. The potential for direct myocardial depression, especially in patients with preexisting left ventricular dysfunction, seems to be greater with this drug than with quinidine and procainamide.

Moricizine

Moricizine is a phenothiazine derivative with modest efficacy in the treatment of sustained ventricular arrhythmias. In view of its proarrhythmic effects, this drug is reserved for the treatment of life-threatening ventricular arrhythmias when other drugs such as amiodarone are not available or contraindicated (eg, allergy). It is not effective in the treatment of atrial arrhythmias. Moricizine decreases the fast inward sodium ion current and also decreases automaticity.

Side Effects

Proarrhythmic effects occur in 3% to 15% of patients treated chronically with moricizine. Patients with poor left ventricular function tolerate moricizine and small increases in systemic blood pressure and heart rate may accompany therapy. Plasma concentrations of theophylline may increase in patients treated with moricizine.

Lidocaine

Lidocaine is used principally for suppression of ventricular arrhythmias, having minimal if any effect on supraventricular tachyarrhythmias (see [Chapter 10](#)). This drug is particularly effective in suppressing reentry cardiac arrhythmias, such as premature ventricular contractions and ventricular tachycardia. The efficacy of prophylactic lidocaine therapy for preventing early ventricular fibrillation after acute myocardial infarction has not been documented and is no longer recommended (see earlier discussion).

In adult patients with a normal cardiac output, hepatic function, and hepatic blood flow, an initial administration of lidocaine, 2 mg/kg IV, followed by a continuous infusion of 1 to 4 mg per minute should provide therapeutic plasma lidocaine concentrations of 1 to 5 $\mu\text{g}/\text{mL}$. Decreased cardiac output and/or hepatic blood flow, as produced by anesthesia, acute myocardial infarction, or congestive heart failure, may decrease by 50% or more of the initial dose and the rate of lidocaine infusion necessary to maintain therapeutic plasma levels. Concomitant administration of drugs such as propranolol and cimetidine can result in decreased hepatic clearance of lidocaine. Advantages of lidocaine over quinidine or procainamide are the more rapid onset and prompt disappearance of effects when the continuous infusion is terminated, greater therapeutic

index, and a much reduced side effect profile. Lidocaine for IV administration differs from that used for local anesthesia because it does not contain a preservative. Lidocaine is also well absorbed after oral administration but is subject to extensive hepatic first-pass metabolism. As a result, only about one-third of an oral dose of lidocaine reaches the circulation. Mexiletine (see the following text) is an oral analogue of lidocaine. Intramuscular (IM) absorption of lidocaine is nearly complete. In an emergency situation, lidocaine, 4 to 5 mg/kg IM, will produce a therapeutic plasma concentration in about 15 minutes. This level is maintained for about 90 minutes.

Mechanism of Action

Lidocaine delays the rate of spontaneous phase 4 depolarization by preventing or diminishing the gradual decrease in potassium ion permeability that normally occurs during this phase. The effectiveness of lidocaine in suppressing premature ventricular contractions reflects its ability to decrease the rate of spontaneous phase 4 depolarization. The ineffectiveness of lidocaine against supraventricular tachyarrhythmias presumably reflects its inability to alter the rate of spontaneous phase 4 depolarization in atrial cardiac cells.

In usual therapeutic doses, lidocaine has no significant effect on either the QRS or QTc interval on the ECG or on atrioventricular conduction. In high doses, however, lidocaine can decrease conduction in the atrioventricular node as well as in the His-Purkinje system.

Metabolism and Excretion

Lidocaine is metabolized in the liver, and resulting metabolites may possess cardiac antiarrhythmic activity.

Side Effects

Lidocaine is essentially devoid of effects on the ECG or cardiovascular system when the plasma concentration remains less than 5 µg/mL. In contrast to quinidine and procainamide, lidocaine does not alter the duration of the QRS complex on the ECG, and activity of the sympathetic nervous system is not changed. Lidocaine depresses cardiac contractility less than any other antiarrhythmic drug used to suppress ventricular arrhythmias. Toxic plasma concentrations of lidocaine (>5-10 µg/mL) produce peripheral vasodilation and direct myocardial depression, resulting in hypotension. In addition, slowing of conduction of cardiac impulses may manifest as bradycardia, a prolonged P-R interval, and widened QRS complex on the ECG. Stimulation of the central nervous system (CNS) occurs in a dose-related manner, with symptoms appearing when plasma concentrations of lidocaine are greater than 5 µg/mL. Seizures are possible at plasma concentrations of 5 to 10 µg/mL. The CNS depression, apnea, and cardiac arrest are possible when plasma lidocaine concentrations are greater than 10 µg/mL. The convulsive threshold for lidocaine is decreased during arterial hypoxemia, hyperkalemia, or acidosis, emphasizing the importance of monitoring these parameters during continuous infusion of lidocaine to patients for suppression of ventricular arrhythmias.

Mexiletine

Mexiletine is an orally effective amine analogue of lidocaine that is used for the chronic suppression of ventricular cardiac tachyarrhythmias. Combination with a β blocker or another antiarrhythmic drug such as quinidine or procainamide results in a synergistic effect that permits a decrease in the dose of mexiletine and an associated decrease in the incidence of side effects. Electrophysiologically, mexiletine is similar to lidocaine. The addition of the amine side group enables mexiletine to avoid significant hepatic first-pass metabolism that limits the effectiveness of orally administered lidocaine. The usual adult dose is 150 to 200 mg every 8 hours. As it is a lidocaine analogue, mexiletine may be effective in decreasing neuropathic pain for patients in whom alternative pain medications have been unsatisfactory.²⁵

Side Effects

Epigastric burning may occur and is often relieved by taking the drug with meals. Neurologic side effects include tremulousness, diplopia, vertigo, and occasionally slurred speech. Cardiovascular side effects resemble lidocaine. Increases in liver enzymes may occur especially in patients manifesting congestive heart

failure. Blood dyscrasias occur rarely. Proarrhythmic effects may manifest in occasionally treated patients. Toxic effects may develop at plasma concentrations only slightly above therapeutic levels.

Tocainide

Tocainide, like mexiletine, is an orally effective amine analogue of lidocaine that was formerly used for the chronic suppression of ventricular cardiac tachyarrhythmias but is no longer available in the United States. Its side effects resemble those of mexiletine, but in rare patients, this drug has caused severe bone marrow depression (leukopenia, anemia, thrombocytopenia) and pulmonary fibrosis.²⁵ The usual adult dose is 400 to 800 mg administered every 8 hours. As with mexiletine, the combination of tocainide with a β -adrenergic blocker or another antiarrhythmic drug has a synergistic effect.

Phenytoin

Phenytoin is particularly effective in suppression of ventricular arrhythmias associated with digitalis toxicity. This drug is effective, although to a lesser extent than quinidine, procainamide, and lidocaine, in the treatment of ventricular arrhythmias due to other causes. Phenytoin may be useful in the treatment of paradoxical ventricular tachycardia or torsades de pointes that is associated with a prolonged QTc interval on the ECG. Treatment of atrial tachyarrhythmias with phenytoin is not very effective.

Phenytoin can be administered orally or IV. The IM administration is too unreliable to treat cardiac arrhythmias. The IV dose is 100 mg (1.5 mg/kg) every 5 minutes until the cardiac arrhythmia is controlled or 10 to 15 mg/kg (maximum 1,000 mg) has been administered. Because phenytoin can precipitate in 5% dextrose in water, it is preferable to give the drug via a delivery tubing containing normal saline. Slow IV injection into a large peripheral or central vein is recommended to minimize the likelihood of discomfort or thrombosis at the injection site. Therapeutic blood levels range from 10 to 18 μ g/mL.

Mechanism of Action

The effects of phenytoin on automaticity and velocity of conduction of cardiac impulses resemble those of lidocaine. Phenytoin exerts a greater effect on the electrocardiographic QTc interval than does lidocaine and shortens the QTc interval more than any of the other antiarrhythmic drugs. Phenytoin has no significant effect on the ST-T waves or the QRS complex. It does not significantly depress the myocardium in usual doses but can cause hypotension when administered in high doses rapidly. Conduction of cardiac impulses through the atrioventricular node is improved, but activity of the sinus node may be depressed. The ability of some volatile anesthetics to depress the sinoatrial node is a consideration if administration of phenytoin during general anesthesia is planned.

Metabolism and Excretion

Phenytoin is hydroxylated and then conjugated with glucuronic acid for excretion in the urine. The elimination half-time is about 24 hours. Because phenytoin is metabolized by the liver, impaired hepatic function may result in higher than normal blood levels of the drug. Blood levels of phenytoin can be lowered by drugs, such as barbiturates, that enhance its rate of metabolism. Warfarin, phenylbutazone, and isoniazid may inhibit metabolism and increase phenytoin blood levels. Uremia increases the unbound fraction of phenytoin relative to the plasma-bound portion.

Side Effects

Phenytoin toxicity most commonly manifests as CNS disturbances, especially cerebellar disturbances. Symptoms include ataxia, nystagmus, vertigo, slurred speech, sedation, and mental confusion. Cerebellar symptoms correlate with phenytoin blood levels of greater than 18 μ g/mL. Cardiac arrhythmias that have not been suppressed at this concentration are unlikely to respond favorably to further increases in the dosage of phenytoin. Phenytoin partially inhibits insulin secretion and may lead to increased blood glucose levels in patients who are hyperglycemic. Leukopenia, granulocytopenia, and thrombocytopenia may occur as a manifestation of drug-induced bone marrow depression. Nausea, skin rash, and megaloblastic anemia may occur.

Flecainide

Flecainide is a fluorinated local anesthetic analogue of procainamide that is more effective in suppressing ventricular premature beats and ventricular tachycardia than quinidine and disopyramide ([Figure 21.5](#)). Flecainide is also effective for the treatment of atrial tachyarrhythmias. Because it delays conduction in the bypass tracts, flecainide can be effective for the treatment of tachyarrhythmias due to reentry mechanisms as associated with the Wolff-Parkinson-White syndrome. Chronic treatment of ventricular arrhythmias with flecainide after myocardial infarction is not recommended due to an increased incidence of sudden death in treated patients.²⁶ Thus, flecainide should be reserved for the treatment of life-threatening arrhythmias.²⁷ This drug is sometimes used to treat arrhythmias in the fetus as it crosses the placenta.²⁷

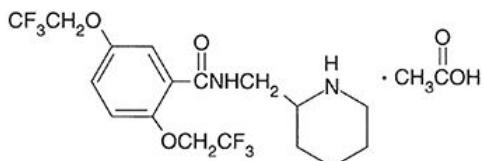


FIGURE 21.5 Flecainide.

Metabolism and Excretion

Oral absorption of flecainide is excellent, and a prolonged elimination half-time (about 20 hours) makes a twice daily dose of 100 to 200 mg acceptable. This drug is not available in an IV formulation. About 25% of flecainide is excreted unchanged by the kidneys, and the remainder appears as weakly active metabolites. Elimination of flecainide is decreased in patients with congestive heart failure or renal failure. Flecainide competes with metabolic pathways used by other drugs and as a result may increase the plasma concentrations of digoxin and propranolol. Coadministration of amiodarone and flecainide can double plasma flecainide concentrations. Phenytoin and other drugs that stimulate hepatic P450 enzymes may speed the elimination of flecainide. The therapeutic plasma concentration of flecainide ranges from 0.2 to 1.0 µg/mL. Flecainide has a moderate negative inotropic effect and a proarrhythmic effect, especially in patients with preexisting decreased left ventricular function. Vertigo and difficulty in visual accommodation are common dose-related side effects of flecainide therapy.

Side Effects

Proarrhythmic effects occur in a significant number of treated patients especially in the presence of left ventricular dysfunction. Flecainide prolongs the QRS complex by 25% or more and, to a lesser extent, prolongs the P-R interval on the ECG. These changes suggest the possibility of atrioventricular or infranodal conduction block of cardiac impulses. Flecainide may depress sinoatrial node function as do β-adrenergic antagonists and calcium channel blockers. For these reasons, flecainide is not administered to patients with second- and third-degree atrioventricular heart block. The most common noncardiac adverse effect of flecainide is dose-related blurred vision. Flecainide increases the capture thresholds of pacemakers. This is the amount of current required to electrically capture cardiac tissue. Therefore, capture thresholds should be remeasured in individuals with pacemakers after the steady-state flecainide dosage is changed.²⁸

Propafenone

Propafenone, like flecainide, is an effective oral antiarrhythmic drug for suppression of ventricular and atrial tachyarrhythmias. This drug possesses weak β-adrenergic blocking and calcium blocking effects. Propafenone may be proarrhythmic, especially in patients with poor left ventricular function and sustained ventricular tachycardia.

Absorption after oral administration is excellent, and peak plasma levels occur in about 3 hours. The rate of metabolism is genetically determined with about 90% of patients able to metabolize propafenone efficiently in the liver. The principal metabolites in those who metabolize the drug rapidly are

pharmacologically active and equivalent in antiarrhythmic potency to the parent drug. Because of extensive metabolism, the availability of propafenone increases significantly in the presence of liver disease.

Side Effects

Proarrhythmic effects are more likely to occur in patients with preexisting ventricular arrhythmias. Propafenone depresses the myocardium and may cause conduction abnormalities such as sinoatrial node slowing, atrioventricular block, and bundle-branch block. Small doses of quinidine inhibit the metabolism of propafenone, whereas propafenone interferes with the metabolism of propranolol and metoprolol resulting in increased plasma concentrations of these β blockers. This drug also increases the plasma concentration of warfarin and may prolong the prothrombin time. Vertigo, disturbances in taste, and blurred vision are the common side effects. Nausea and vomiting may occur, and, rarely, cholestatic hepatitis or worsening of asthma manifests.

β -Adrenergic Antagonists

β -Adrenergic antagonists are effective for treatment of cardiac arrhythmias related to enhanced activity of the sympathetic nervous system (perioperative stress, thyrotoxicosis, pheochromocytoma). Propranolol and esmolol are effective for controlling the rate of ventricular response in patients with atrial fibrillation and atrial flutter. Multifocal atrial tachycardia may respond to esmolol or metoprolol but is best treated with amiodarone. Comparable doses of metoprolol (5-15 mg IV over 20 minutes, which lasts 5-7 hours) produces antiarrhythmic effects similar to those of propranolol as well as the same potential side effects. Acebutolol is effective in the treatment of frequent premature ventricular contractions. β -Adrenergic antagonists, especially propranolol, may be effective in controlling torsades de pointes for patients with prolonged QTc intervals. Acebutolol, propranolol, and metoprolol are approved for prevention of sudden death following myocardial infarction. For example, in contrast to class I antiarrhythmic drugs, propranolol decreases sudden death as well as reinfarction rates in the first year after acute myocardial infarction.¹⁶

Mechanism of Action

The antiarrhythmic effects of β -adrenergic antagonists most likely reflect blockade of the responses of β receptors in the heart to sympathetic nervous system stimulation as well as the effects of circulating catecholamines. As a result, the rate of spontaneous phase 4 depolarization and sinoatrial node discharge is decreased. The rate of conduction of cardiac impulses through the atrioventricular node is slowed as reflected by a prolonged P-R interval on the ECG. This drug has little effect on the ST-T wave, although it may shorten the overall QTc interval. β -Adrenergic antagonists can depress the myocardium not only by β blockade but also by direct depressant effects on cardiac muscle. In addition to β -adrenergic blockade, these drugs cause alterations in the electrical activity of myocardial cells. This cell membrane effect is probably responsible for some of the antidysrhythmic effects of β -adrenergic antagonists. Indeed, dextropropranolol, which lacks β -adrenergic antagonist activity, is an effective cardiac antiarrhythmic.

The usual oral dose of propranolol for chronic suppression of ventricular arrhythmias is 10 to 80 mg every 6 to 8 hours. The total daily dose is determined by the physiologic effects of propranolol on the heart rate and systemic blood pressure. Effective β blockade is usually achieved in an otherwise normal person when the resting heart rate is 55 to 60 beats per minute. For emergency suppression of cardiac arrhythmias in an adult, propranolol may be administered IV in a dose of 1 mg per minute (3-6 mg). The onset of action after IV administration is within 2 to 5 minutes, the peak effect at the atrioventricular node is within 10 to 15 minutes, and the duration of action is 3 to 4 hours. Administration at 1-minute intervals is intended to minimize the likelihood of excessive pharmacologic effects on the conduction of cardiac impulses. In patients with marginal systemic blood pressure or left ventricular dysfunction, the rate of administration may need to be slowed and the total dose limited to less than 3 mg.

Metabolism and Excretion

Orally administered propranolol is extensively metabolized in the liver, and a hepatic first-pass effect is responsible for the variation in plasma concentration; the therapeutic plasma concentration of propranolol

may vary from 10 to 30 ng/mL. Propranolol readily crosses the blood–brain barrier. The principal metabolite of propranolol is 4-hydroxypropranolol, which possesses weak β -adrenergic antagonist activity. This active metabolite most likely contributes to the antiarrhythmic activity after the oral administration of propranolol. The elimination half-time of propranolol is 2 to 4 hours, although the antiarrhythmic activity usually persists for 6 to 8 hours.

Side Effects

Bradycardia, hypotension, myocardial depression, and bronchospasm are side effects of β -adrenergic antagonists that reflect the ability of these drugs to inhibit sympathetic nervous system activity. Patients with any degree of congestive heart failure are highly dependent on increased sympathetic nervous system activity as a compensatory mechanism. Attenuation of this compensatory response may accentuate congestive heart failure. In addition, the direct depressant effects of propranolol on myocardial contractility may further accentuate congestive heart failure. The use of propranolol in patients with preexisting atrioventricular heart block is not recommended. Propranolol may cause drug fever, an allergic rash, or nausea and may increase esophageal reflux. Cold extremities and worsening of Raynaud disease may occur. Interference with glucose metabolism may manifest as hypoglycemia in patients being treated for diabetes mellitus. The most common CNS side effects are mental depression and fatigue. Reversible alopecia may occur. Upregulation of β -adrenergic receptors occurs with chronic administration of β -adrenergic antagonists such that abrupt discontinuation of treatment may lead to supraventricular tachycardia that is particularly undesirable in patients with coronary artery disease. Slowly tapering the dose of β -adrenergic antagonist will prevent withdrawal responses.

Amiodarone

Amiodarone is a potent antiarrhythmic drug with a wide spectrum of activity against refractory supraventricular and ventricular tachyarrhythmias. In the presence of ventricular tachycardia or fibrillation that is resistant to electrical defibrillation, amiodarone 300 mg IV is recommended. Preoperative oral administration of amiodarone decreases the incidence of atrial fibrillation after cardiac surgery.²⁹ It is also effective for suppression of tachyarrhythmias associated with Wolff-Parkinson-White syndrome because it depresses conduction in the atrioventricular node and the accessory bypass tracts. Similar to β blockers and unlike class I drugs, amiodarone decreases mortality after myocardial infarction.³⁰

After initiation of oral therapy, a decrease in ventricular tachyarrhythmias occurs within 72 hours. The maintenance dose can usually be gradually decreased to about 400 mg daily for suppression of ventricular tachyarrhythmias and 200 mg daily for suppression of supraventricular tachyarrhythmias. Administered IV over 2 to 5 minutes, a dose of 5 mg/kg produces a prompt antiarrhythmic effect that lasts up to 4 hours. Therapeutic blood concentrations of amiodarone are 1.0 to 3.5 $\mu\text{g}/\text{mL}$. After discontinuation of chronic oral therapy, the pharmacologic effect of amiodarone lasts for a prolonged period (up to 60 days), reflecting the prolonged elimination half-time of this drug.

Mechanism of Action

Amiodarone, a benzofuran derivative, is 37% iodine by weight and structurally resembles thyroxine ([Figure 21.6](#)). It prolongs the effective refractory period in all cardiac tissues, including the sinoatrial node, atrium, atrioventricular node, His-Purkinje system, ventricle, and, in the case of Wolff-Parkinson-White syndrome, accessory bypass tracts. Amiodarone has an antiadrenergic effect (noncompetitive blockade of α and β receptors) and a minor negative inotropic effect, which may be offset by the drug's potent vasodilating properties.³¹ Amiodarone acts as an antianginal drug by dilating coronary arteries and increasing coronary blood flow.

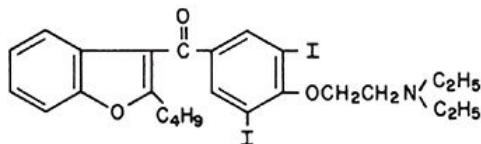


FIGURE 21.6 Amiodarone.

Metabolism and Excretion

Amiodarone has a prolonged elimination half-time (29 days) and large volume of distribution ([Figure 21.7](#)).³² This drug is minimally dependent on renal excretion as evidenced by an unchanged elimination half-time in the absence of renal function.³² The principal metabolite, desethylamiodarone, is pharmacologically active and has a longer elimination half-time than the parent drug, resulting in accumulation of this metabolite with chronic therapy. Protein binding of amiodarone is extensive, and the drug is not easily removed by hemodialysis. There is an inconsistent relationship between the plasma concentration of amiodarone and its pharmacologic effects as the ultimate concentration of drug in the myocardium is 10 to 50 times that present in the plasma.

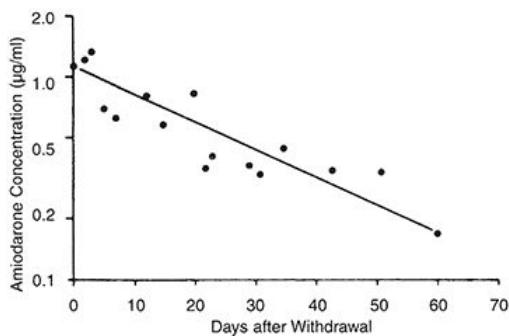


FIGURE 21.7 After discontinuation of amiodarone, the plasma concentration decreases slowly, resulting in a prolonged elimination half-time. *From Kannan R, Nademanee K, Hendrickson JA, et al. Amiodarone kinetics after oral doses. Clin Pharmacol Ther. 1982;31(4):438-444. Copyright © 1982 American Society for Clinical Pharmacology and Therapeutics. Reprinted by permission of John Wiley & Sons, Inc.*

Side Effects

Side effects in patients treated chronically with amiodarone are common, especially when the daily maintenance dose exceeds 400 mg.³³ Screening tests, such as chest radiographs and tests for pulmonary function, thyroid-stimulating hormone, and liver function, are recommended. Other than the pulmonary function tests, these studies should be repeated at 3, 6, and 12 months and annually thereafter.³⁴

Pulmonary Toxicity

The most serious side effect of amiodarone is pulmonary alveolitis (pneumonitis).^{35,36} The overall incidence of amiodarone-induced pulmonary toxicity is estimated at 5% to 15% of treated patients, with a reported mortality of 5% to 10%. The cause of this drug-induced pulmonary toxicity is not known but may reflect the ability of amiodarone to enhance production of free oxygen radicals in the lungs that in turn oxidize cellular proteins, membrane lipids, and nucleic acids. It is suggested that high-inspired oxygen concentrations may accelerate these reactions.³⁷ For this reason, it may be prudent to restrict the inspired concentration of oxygen in patients receiving amiodarone and undergoing general anesthesia to the lowest level capable of maintaining adequate systemic oxygenation.³⁸ Indeed, postoperative pulmonary edema has been reported in patients being treated chronically with amiodarone.³⁸ Furthermore, there is evidence that patients with preexisting evidence of amiodarone-induced pulmonary toxicity are at increased risk for developing adult respiratory distress syndrome after surgery that requires cardiopulmonary bypass.^{39,40} It must be recognized, however, that no animal model has established a cause-and-effect relationship between oral amiodarone administration and secondary oxygen-enhanced pulmonary toxicity.

There are two distinct types of presentation of patients with amiodarone-induced pulmonary toxicity.³⁶ The more common form of pulmonary toxicity consists of a slow insidious onset of progressive dyspnea,

cough, weight loss, and pulmonary infiltrates on the chest x-ray. The second form of pulmonary toxicity has a much more acute onset of dyspnea, cough, arterial hypoxemia, and occasionally fever that may mimic an infectious pneumonia. Postoperative pulmonary edema attributed to amiodarone-induced pulmonary toxicity reflects this acute form of onset.

Cardiovascular

Like quinidine and disopyramide, amiodarone may prolong the QTc interval on the ECG, which may lead to an increased incidence of ventricular tachyarrhythmias, including torsades de pointes (proarrhythmic effect). Heart rate often slows and is resistant to treatment with atropine. Responsiveness to catecholamines and sympathetic nervous system stimulation is decreased as a result of drug-induced inhibition of α - and β -adrenergic receptors. Direct myocardial depressant effects are presumed to be minimal.⁴¹ The IV administration of amiodarone may result in hypotension, most likely reflecting the peripheral vasodilating effects of this drug. Atrioventricular heart block may also occur when the drug is administered IV. The negative inotropic effects of amiodarone may be enhanced in the presence of general anesthesia, β -adrenergic blockers, and calcium channel blockers.⁴² Drugs that inhibit automaticity of the sinoatrial node (lidocaine) could accentuate the effects of amiodarone and increase the likelihood of sinus arrest. The potential need for a temporary artificial cardiac (ventricular) pacemaker and administration of a sympathomimetic such as isoproterenol may be a consideration in patients being treated with this drug and scheduled to undergo surgery.⁴³

Ocular, Dermatologic, Neurologic, and Hepatic

Corneal microdeposits occur in most patients during amiodarone therapy, but visual impairment is unlikely. Optic neuropathy has been found in 1.8% of patients treated with amiodarone compared to 0.3% of the general population.⁴⁴ Optic neuropathy from amiodarone typically has a more insidious onset, milder degree of visual loss, longer duration of disc edema, and more often bilateral. Discontinuation often leads to slow improvement in visual acuity. Photosensitivity and rash develop in up to 10% of patients. Rarely, there may be a cyanotic discoloration (slate-gray pigmentation) of the face that persists even after the drug is discontinued. Neurologic toxicity may manifest as peripheral neuropathy, tremors, sleep disturbance, headache, or proximal skeletal muscle weakness.⁴⁵ Transient, mild increases in plasma transaminase concentrations may occur, and fatty liver infiltration has been observed.⁴⁵

Pharmacokinetic

Amiodarone inhibits hepatic P450 enzymes resulting in increased plasma concentrations of digoxin, procainamide, quinidine, warfarin, and cyclosporine. Amiodarone also displaces digoxin from protein-binding sites. The digoxin dose may be decreased as much as 50% when administered in the presence of amiodarone. Amiodarone also increases the plasma concentrations of quinidine, procainamide, and phenytoin. The anticoagulant effects of warfarin are potentiated because amiodarone may directly depress vitamin K-dependent clotting factors.

Endocrine

Amiodarone contains iodine and has effects on thyroid metabolism, causing either hypothyroidism or hyperthyroidism in 2% to 4% of patients. Thyroid dysfunction may develop insidiously in these patients. Hyperthyroidism has occurred up to 5 months after discontinuation of amiodarone. Patients with preexisting thyroid dysfunction seem more likely to develop amiodarone-related alterations in thyroid function. Hyperthyroidism is best detected by finding an increased plasma concentration of triiodothyronine. Hypothyroidism is best detected by finding an increased plasma concentration of thyroid-stimulating hormone.

Amiodarone-induced hyperthyroidism reflecting the release of iodine from the parent drug is often refractory to conventional therapy. These patients may be intolerant of β -adrenergic blockade because of their underlying cardiomyopathies. When medical management fails, the performance of surgical thyroidectomy

provides prompt metabolic control. Bilateral superficial cervical plexus blocks have been described for anesthetic management of subtotal thyroidectomy in these patients.⁴⁶

Dronedarone

Dronedarone is a noniodinated benzofuran derivative of amiodarone that has been developed as an alternative for the treatment of atrial fibrillation and atrial flutter. Similar to amiodarone, dronedarone is a potent blocker of multiple ion currents and is currently recommended for treatment of atrial fibrillation and atrial flutter in people whose hearts have either returned to normal rhythm or who undergo drug therapy or direct current cardioversion to maintain normal rhythm. Dronedarone reduced the rate of hospitalization in atrial fibrillation patients but did not demonstrate a reduction in mortality.⁴⁷ A trial of the drug in heart failure was stopped as an interim analysis showed a possible increase in heart failure deaths in patients with moderate to severe congestive heart failure.⁴⁸ As a result, the clinical utility of dronedarone is significantly limited by its efficacy and contraindication in patients with permanent atrial fibrillation or patients with advanced or recent congestive heart failure exacerbations.

Mechanism of Action

Dronedarone blocks the L-type calcium current, the inward sodium current, and multiple potassium currents. It also has sympatholytic effects.⁴⁹ However, it is a more potent blocker of peak sodium current and has stronger in vitro antiadrenergic effects compared with amiodarone.

Metabolism and Excretion

Dronedarone is well absorbed (70%-94%) after oral administration, and absorption increases two- to threefold when it is taken with food. Dronedarone undergoes significant first-pass metabolism that reduces its net bioavailability to 15%. With sustained administration of 400 mg twice daily, steady-state plasma concentrations of 84 to 167 ng/mL are reached in 7 days. The clearance of dronedarone is principally nonrenal, with a terminal half-life of 20 to 40 hours. Dronedarone is a substrate for and a moderate inhibitor of CYP3A4. Consequently, dronedarone should not be coadministered with other CYP3A4 inhibitors such as antifungals, macrolide antibiotics, or protease inhibitors. When coadministered with moderate CYP3A4 inhibitors such as verapamil and diltiazem, lower doses of concomitant drugs should be used to avoid severe bradycardia and conduction block.⁴⁹

Side Effects

The most frequently reported adverse effect of dronedarone is nausea and diarrhea. As compared to placebo, patients in the treatment group of the ATHENA trial had significantly increased rates of bradycardia, QT interval prolongation, diarrhea, nausea, and serum creatinine increase. In the ATHENA trial, patients in the treatment group did not have increased rates of interstitial lung disease, hyperthyroid, or hypothyroidism.⁵⁰

Sotalol

Sotalol is a nonselective β-adrenergic antagonist drug at low doses, and at higher doses, it prolongs the cardiac action potential in the atria, ventricles, and accessory bypass tracts. Sotalol is administered for the treatment of sustained ventricular tachycardia or ventricular fibrillation.⁵¹ This drug is also approved for the treatment of atrial tachyarrhythmia including atrial fibrillation as may follow cardiac surgery. Sotalol is not recommended in patients with asthma, left ventricular dysfunction, and cardiac conduction abnormalities including prolonged QTc intervals on the ECG. Because of its proarrhythmic effects, this drug is usually restricted for use in patients with life-threatening ventricular arrhythmias.

The daily oral dose of sotalol is 240 to 320 mg administered twice daily. Because sotalol is excreted mainly by the kidneys, the dosing intervals should be lengthened in patients with renal dysfunction. Sotalol does not bind to plasma proteins, is not metabolized, and does not cross the blood-brain barrier to any extent. β-Adrenergic blocking effects of this drug primarily reflect activity of the levorotatory isomer.

Side Effects

The most dangerous side effect of sotalol is torsades de pointes, reflecting prolongation of the QTc interval on the ECG. Torsades de pointes is dose related, occurring in 0.5% of patients receiving 80 mg of sotalol daily and in 5.8% of patients receiving more than 320 mg daily. The β -blocking effects of sotalol result in decreased myocardial contractility, bradycardia, and delayed conduction of cardiac impulses through the atrioventricular node. Other side effects of sotalol include fatigue, dyspnea, vertigo, and nausea.

Ibutilide

Ibutilide is effective for the conversion of recent onset atrial fibrillation or atrial flutter to normal sinus rhythm. Hepatic metabolism is extensive with production of inactive metabolites with the exception of hydroxy metabolites that possess weak antiarrhythmic effects. Polymorphic ventricular tachycardia with or without prolongation of the QTc interval on the ECG may occur during ibutilide treatment, especially in patient with predisposing factors (impaired left ventricular function, preexisting prolonged QTc intervals, hypokalemia, hypomagnesemia).

Dofetilide

Dofetilide is a potent, pure potassium channel blocking drug of the class III antiarrhythmic drugs. Dofetilide causes a dose-dependent prolongation of the action potential duration and hence the QT interval. Dofetilide is effective for the conversion of recent onset atrial fibrillation or atrial flutter to normal sinus rhythm as well as the maintenance of normal sinus rhythm in patients who have been successfully cardioverted. Oral absorption is greater than 90%, and 80% of the drug is excreted unchanged in the urine. The starting dose of 0.5 mg twice daily is the highest acceptable dose. Dosage adjustments are indicated based on renal function. Trimethoprim, cimetidine, and prochlorperazine can inhibit renal clearance of dofetilide. Proarrhythmic effects of dofetilide may occur when it is coadministered with calcium channel blocking drugs. Dofetilide does not depress myocardial contractility. Torsades de pointes occurs in a dose-related manner, especially in patients with preexisting left ventricular dysfunction. By FDA mandate, a patient must be admitted to a certified hospital for at least 72 hours for cardiac monitoring during initiation of dofetilide. Such monitoring is necessary to determine the presence of QT prolongation.

Verapamil and Diltiazem

Among the calcium channel blockers, verapamil and diltiazem have the greatest efficacy for the treatment of cardiac arrhythmias.¹ Verapamil is highly effective in terminating paroxysmal supraventricular tachycardia, a reentrant tachycardia whose pathway usually includes the atrioventricular node. This drug also effectively controls the ventricular rate in most patients who develop atrial fibrillation or flutter. Verapamil, however, does not have a depressant effect on accessory tracts and thus will not slow the ventricular response rate in patients with Wolff-Parkinson-White syndrome. In fact, verapamil may cause reflex sympathetic nervous system activity that enhances conduction of cardiac impulses over accessory tracts and thus increases the ventricular response rate similar to digitalis. Verapamil has little efficacy in the therapy for ventricular ectopic beats.

The usual dose of verapamil for suppression of paroxysmal supraventricular tachycardia is 5 to 10 mg IV (75-150 μ g/kg) over 1 to 3 minutes followed by a continuous infusion of about 5 μ g/kg per minute to maintain a sustained effect. The administration of calcium gluconate, 1 g IV, approximately 5 minutes before administration of verapamil may decrease verapamil-induced hypotension without altering the drug's antiarrhythmic effects.⁵² Chronic treatment with oral verapamil, 80 to 120 mg every 6 to 8 hours, may be useful for prevention of paroxysmal supraventricular tachycardia and for control of the ventricular response rate in atrial fibrillation or atrial flutter. Diltiazem, 20 mg IV, produces antiarrhythmic effects similar to those of diazepam, and the potential side effects are similar.

Mechanism of Action

Verapamil and the other calcium channel blockers inhibit the flux of calcium ions across the slow channels of vascular smooth muscle and cardiac cells. This effect on calcium ion flux manifests as a decreased rate of spontaneous phase 4 depolarization. Verapamil has a substantial depressant effect on the atrioventricular node

and a negative chronotropic effect on the sinoatrial node. This drug exerts a negative inotropic effect on cardiac muscle and produces a moderate degree of vasodilation of the coronary arteries and systemic arteries.

Metabolism and Excretion

An estimated 70% of an injected dose of verapamil is eliminated by the kidneys, whereas up to 15% may be present in the bile. A metabolite, norverapamil, may contribute to the parent drug's antiarrhythmic effects. The need for a large oral dose is related to the extensive hepatic first-pass effect that occurs with the oral route of administration.

Side Effects

The side effects of verapamil used to treat cardiac arrhythmias reflect its effects on calcium ion flux into cardiac cells. Atrioventricular heart block is more likely in patients with preexisting defects in the conduction of cardiac impulses. Direct myocardial depression and decreased cardiac output are likely to be exaggerated in patients with poor left ventricular function. Peripheral vasodilation may contribute to hypotension. There may be potentiation of anesthetic-produced myocardial depression, and the effects of neuromuscular blocking drugs may be exaggerated.

By decreasing hepatic blood flow, cimetidine may increase the plasma concentration of verapamil. Verapamil, like quinidine, may increase the plasma concentration of digoxin by 50% to 75%. Excessive bradycardia has been observed when verapamil and propranolol are administered simultaneously.

Other Cardiac Antiarrhythmic Drugs

Digitalis

Digitalis preparations such as digoxin are effective cardiac antiarrhythmics for stabilization of atrial electrical activity and the treatment and prevention of atrial tachyarrhythmias. Because of their vagolytic effects, these drugs can also slow conduction of cardiac impulses through the atrioventricular node and thus slow the ventricular response rate in patients with atrial fibrillation. Conversely, digitalis preparations enhance conduction of cardiac impulses through accessory bypass tracts and can dangerously increase the ventricular response rate in patients with Wolff-Parkinson-White syndrome. The usual oral dose of digoxin is 0.5 to 1.0 mg in divided doses over 12 to 24 hours. Digitalis toxicity is a risk and may manifest as virtually any cardiac arrhythmia (most commonly atrial tachycardia with block).

Adenosine

Adenosine is an endogenous nucleoside that slows conduction of cardiac impulses through the atrioventricular node, making it an effective alternative to calcium channel blockers (verapamil) for the acute treatment of paroxysmal supraventricular tachycardia, including that due to conduction through accessory pathways in patients with Wolff-Parkinson-White syndrome.⁵³ This drug is not effective in the treatment of atrial fibrillation, atrial flutter, or ventricular tachycardia. The usual dose of adenosine is 6 mg IV followed, if necessary, by a repeat injection of 6 to 12 mg IV about 3 minutes later.

Adenosine receptors represent a logical target for treatment of pain. Adenosine agonists result in blockade of acute nociception and reduce hypersensitivity to thermal or mechanical stimuli in the presence of sensitization after peripheral inflammation or nerve injury. This response most likely reflects actions on extracellular G protein-coupled receptors present in the periphery nervous system and CNS, primarily in the spinal cord. Intrathecal administration of adenosine produces selective inhibition of hypersensitivity presumed to be due to central sensitization.⁵⁴

Mechanism of Action

Adenosine has cardiac electrophysiologic effects similar to those of the calcium channel blockers verapamil and diltiazem.¹ It stimulates cardiac adenosine₁ receptors to increase potassium ion currents, shorten the action potential duration, and hyperpolarize cardiac cell membranes. In addition, adenosine decreases cyclic adenosine monophosphate concentrations. Its short-lived cardiac effects (elimination half-time 10 seconds)

are due to carrier-mediated cellular uptake and metabolism to inosine by adenosine deaminase. Methylxanthines inhibit the actions of adenosine by binding to adenosine₁ receptors. Conversely, dipyridamole (adenosine uptake inhibitor) and cardiac transplantation (denervation hypersensitivity) potentiate the effects of adenosine.

Side Effects

The side effects associated with the rapid IV administration of adenosine include facial flushing, headache, dyspnea, chest discomfort, and nausea. Adenosine may produce transient atrioventricular heart block. Bronchospasm, although an uncommon complication, has been observed after the IV administration of adenosine, even in the absence of preexisting symptoms.^{55,56} It is recommended that adenosine be used with caution, if at all, in patients known to have active wheezing. Several theories have been proposed to account for adenosine's bronchoconstrictor effect, including activation of adenosine receptors on the bronchial smooth muscle, mast cell degranulation, and stimulation of prostaglandin formation.⁵⁷ The pharmacologic effects of adenosine are antagonized by methylxanthines (theophylline, caffeine) and potentiated by dipyridamole.

Ranolazine

Although developed as treatment for angina, ranolazine has been noted to have efficacy in treatment of atrial arrhythmias and suppression of nonsustained ventricular tachycardia. Ranolazine is a piperazine derivative with a chemical structure similar to lidocaine. The cellular effects of ranolazine are attributed to binding at the local anesthetic binding site of the voltage-gated sodium channel. It is currently approved for the adjunctive treatment of chronic stable angina; however, multiple ongoing studies are evaluating the efficacy and safety of ranolazine in treatment of atrial fibrillation.

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Diuretics*

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Diuretics, commonly used in the treatment of hypertension and heart failure, consist of a group of drugs with different pharmacokinetic and pharmacodynamic properties. Their primary effect is to increase urine flow. Most diuretics produce their clinical effect by blocking sodium (Na) reabsorption in different locations of the nephron.¹ This results in increased Na delivery to the distal tubules. The normal driving force for potassium (K) excretion by distal renal tubules is the transtubular electrical potential difference created by Na reabsorption. The presence of Na in the distal tubules promotes the reabsorption of Na in exchange for secretion of K, therefore resulting in hypokalemia. Individual sites of action of the different diuretics are illustrated in [Figure 22.1](#). In general, diuretics with a site of action upstream of the collecting duct result in hyponatremia, hypokalemia, and metabolic alkalosis. In contrast, collecting duct diuretics result in hyperkalemia and metabolic acidosis.²

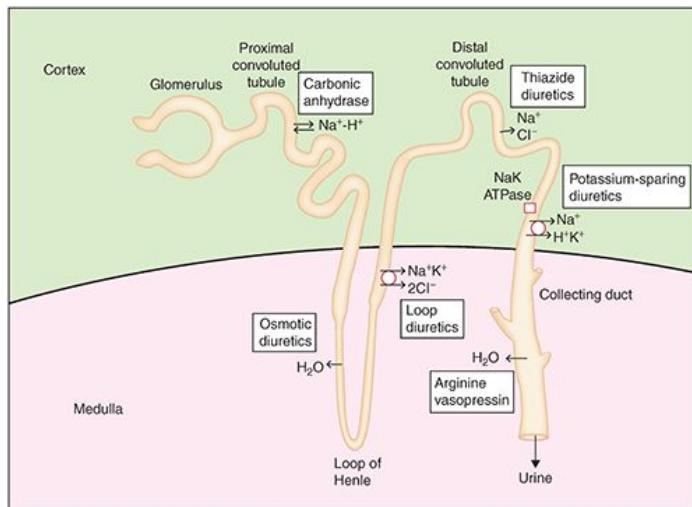


FIGURE 22.1 The sites of action of the different diuretics.

Carbonic Anhydride Inhibitors

Acetazolamide is the prototype of a class of sulfonamide drugs that bind avidly to carbonic anhydrase enzyme, producing noncompetitive inhibition of enzyme activity, principally in the proximal renal tubules, as well as the collecting ducts (see [Figure 22.1](#); [Table 22.1](#)).³ A Na-hydrogen (H) exchanger allows absorption of Na in exchange for secretion of H+ into the renal tubule.

TABLE 22.1

Diuretics and their sites of action

	Receptors	Main site of action	Clinical uses	Notable side effects
Carbonic anhydrase	Carbonic anhydrase	Proximal convoluted tubule	Altitude sickness Glaucoma	Metabolic acidosis
Loop diuretics	Na-K-2Cl cotransport	Medullary thick ascending loop of Henle	First-line diuretics in renal impairment	Ototoxicity Alkalosis Hypokalemia

Thiazides	Na-Cl cotransport	Cortical ascending loop of Henle	First-line therapy of hypertension	Alkalosis Hypokalemia Diabetes and dyslipidemia Hyperuricemia
Osmotic diuretics		Proximal convoluted tubule and loop of Henle	Increased intracranial pressure Oxygen free radical scavenging	Volume overload in CHF patients Hypokalemia, hyponatremia, hypomagnesemia
Potassium-sparing diuretics	Epithelial Na channel	Collecting duct	Adjuncts to loop diuretics or thiazides	Hyperkalemia
Aldosterone blockers	Na-K-ATPase	Collecting duct	Heart failure with low ejection fraction	Hyperkalemia
Dopamine and fenoldopam	D ₁	Proximal tubule and loop of Henle	Renal protection and hypertension treatment in critically ill patients	Effectiveness not substantiated
Brain natriuretic peptide	Na-K-ATPase	Collecting duct	Management of decompensated heart failure	
Vasopressin	V ₂	Collecting duct	SIADH, CHF, cirrhosis	Osmotic demyelination
Aquaporins	AQP	Collecting duct		

Abbreviations: AQP, aquaporin; ATPase, adenosine triphosphatase; CHF, congestive heart failure; Cl, chlorine; 2Cl, 2 units of chlorine ions; K, potassium; Na, sodium; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

Bicarbonate (HCO_3^-) and H^+ combine in the proximal tubule lumen to produce carbonic acid. Carbonic anhydrase enzyme catalyzes the otherwise slow breakdown of carbonic acid into carbon dioxide (CO_2) and water; CO_2 diffuses readily into the tubular cells, where cytoplasmic carbonic anhydrase catalyzes the reverse reaction leading to HCO_3^- , which then follows an electrochemical gradient across the basal membrane into the interstitium. The net result is absorption of HCO_3^- . Inhibition of carbonic anhydrase in the proximal renal tubule results in decreased reabsorption of Na^+ , HCO_3^- , and water.³

Pharmacokinetics and Pharmacodynamics

After oral administration, acetazolamide is excreted unchanged by the kidneys. The dose should be adjusted in patients with renal failure and the elderly.⁴

Acetazolamide completely blocks membrane-bound and cytoplasmic carbonic anhydrase in the proximal tubule and to a lesser extent, in the collecting ducts, preventing Na and HCO_3^- absorption.³ This increased excretion of HCO_3^- results in an alkaline urine with metabolic acidosis. Natriuresis associated with carbonic anhydrase inhibitors is modest, with a fractional Na excretion of up to 5%.³ The increased delivery of Na to the distal tubules leads to K loss. Most of the chloride is reabsorbed in the loop of Henle.³ This leads to the excretion of an alkaline urine in the presence of hyperchloremic metabolic acidosis.

Clinical Uses

In addition to its diuretic properties, acetazolamide is administered to decrease intraocular pressure in the treatment of glaucoma. There is a high concentration of carbonic anhydrase enzyme in the ciliary process; inhibition of the enzyme activity by acetazolamide results in decreased formation of aqueous humor and, consequently, decreased intraocular pressure.² Similarly, formation of cerebrospinal fluid is also inhibited by

acetazolamide. Accordingly, acetazolamide has been used in the treatment of idiopathic intracranial hypertension.² Idiopathic intracranial hypertension, previously referred to as **benign intracranial hypertension** or **pseudotumor cerebri**, is caused by increased intracranial pressure in the absence of tumors or other causes. It manifests with headaches, pulsatile tinnitus, and visual changes secondary to papilledema, which could progress to vision loss. Women are more likely affected, especially women with obesity, in their third decade of life. When treatment with acetazolamide fails, surgical treatment is an option. In addition, lumbar punctures, in addition to being diagnostic, provide symptomatic relief.

Acetazolamide may be beneficial in the management of familial periodic paralysis because the drug-induced metabolic acidosis increases the local concentration of K in skeletal muscles.² Similarly, acetazolamide, by producing metabolic acidosis, may stimulate the respiratory drive in patients who are hypoventilating in a compensatory response to respiratory alkalosis, such as altitude sickness. Altitude sickness, which can be prevented by a slow acclimatization process, develops following rapid ascent to high altitudes.² The hypoxia at high altitudes is counteracted by hyperventilation, which leads to respiratory alkalosis. This in turn depresses ventilation. Acetazolamide-induced metabolic acidosis can reverse the hypoventilation.² Conversely, the loss of HCO₃⁻ ions necessary to buffer CO₂ may result in the exacerbation of respiratory acidosis in patients with chronic obstructive airway disease, leading to central nervous system depression.

Side Effects

There is a high incidence of systemic side effects associated with the use of acetazolamide such as fatigue, decreased appetite, depression, and paresthesias,⁴ which could be secondary to the development of acidosis.⁴

Acetazolamide dose should be reduced in patients with chronic renal insufficiency and avoided in patients with severe chronic renal insufficiency because of the increased risk of metabolic acidosis.²

Loop Diuretics

Furosemide, torsemide, azosemide, bumetanide, and ethacrynic acid are diuretics that inhibit reabsorption of Na, K, and chloride by impairing activity of the Na-K-2Cl transport protein in the medullary portions of the thick ascending limb of the loop of Henle. This area of the nephron accounts for the reabsorption of 20% to 30% of filtered Na while being impermeable to water.^{1,2} Because of their site of action, loop diuretics are the most potent diuretics, with a dose-dependent response.² Diuretics in general, and loop diuretics in particular, are first-line therapy in patients with fluid retention resulting from heart failure.²

Pharmacokinetics and Pharmacodynamics

Ethacrynic Acid

Ethacrynic acid is the only nonsulfonamide in the group and can therefore be used in those allergic to other drugs in this class. It has 70% the relative potency of furosemide.³ Ototoxicity, a common dose-dependent side effect of loop diuretics, is notable with the use of ethacrynic acid.² In addition, nausea is common following administration of ethacrynic acid.

Furosemide

Furosemide is effective when administered orally or intravenously (IV). However, absorption of orally administered furosemide varies between patients from 10% to 100%, with an average of 50%.^{2,5} Protein binding is extensive, with approximately 90% of the drug bound to albumin. Glomerular filtration and renal tubular secretion account for approximately 50% to 60% of furosemide excretion. The remaining 40% to 50% is conjugated to glucuronide in the kidneys.^{2,5,6} The elimination half-life is 1 to 2 hours, resulting in the short duration of action of furosemide. Furosemide has a fast onset of action, producing diuresis within 5 to 10 minutes of administration, with a peak effect at 30 minutes and duration of action of 2 to 6 hours. In order to achieve natriuresis, a specific dose of the diuretic should reach the site of action within the kidneys. In patients with normal renal function, 40 mg of IV furosemide will produce maximal natriuresis.⁵ Because of decreased drug delivery to the tubule in chronic renal insufficiency, the dosing of loop diuretics should be

increased.^{2,5} In these patients, maximal diuresis can be achieved with an IV bolus of 160 to 200 mg, administered slowly to avoid the occurrence of tinnitus.⁵ Doses larger than 200 mg will not result in increased natriuresis.⁵ In addition, in patients with chronic renal insufficiency, a loading dose followed by a continuous infusion of furosemide could be considered instead of repeated bolus administration.^{1,5} However, the Diuretic Optimization Strategies Evaluation trial, a prospective randomized study of the use of loop diuretics in patients admitted with acute heart failure, did not find a significant difference in symptomatic relief or significant improvement of renal function with the use of high-dose diuretics or with continuous diuretic infusion compared to low-dose or repeated diuretic boluses, respectively.⁷ Alternatively, the addition of a different class of diuretics, such as thiazide diuretics can help in this setting.⁵

Bumetanide and Torsemide

Bumetanide has a bioavailability of 80% to 100% after oral administration. It can be administered orally, IV, or intramuscularly. It is 40 times more potent than furosemide except in its effect on K excretion.² Similar to bumetanide, torsemide's metabolism is mostly by the liver,² and in patients with liver failure, there is increased drug delivery to the kidneys.⁵ Torsemide is 3 times as potent as furosemide and has a longer duration of action, with a plasma half-life of 3 to 4 hours,³ allowing for a once-a-day dosing regimen.⁸

Clinical Uses

Loop diuretics are not first-line treatment for hypertension in patients with normal kidney function. However, they are first-line diuretics in patients with renal insufficiency.^{1,5,8} The antihypertensive effect of loop diuretics is due to their ability to decrease intravascular fluid volume and eliminate salt. Compared to furosemide, the long-acting drug azosemide produces better blood pressure control, especially at nighttime.¹ This effect is desirable since the lack of nocturnal fall in blood pressure (nondipping) is associated with end-organ damage.¹

Loop diuretics are commonly used in patients admitted with acute exacerbation of heart failure.^{7,8} Diuresis leads to loss of water and salt with a resulting decrease in intravascular volume thus decreasing ventricular filling pressure and reducing pulmonary edema.⁶ In addition, loop diuretics mediate peripheral vasodilation via prostaglandins, further decreasing venous return and pulmonary edema.⁶ Treatment with torsemide was found to decrease readmissions related to heart failure when compared to furosemide.¹

Furosemide decreases intracranial pressure by inducing systemic diuresis and by decreasing cerebrospinal fluid production. This diuretic-induced decrease in intracranial pressure is not accompanied by changes in cerebral blood flow or plasma osmolarity. Furosemide can be administered as single-drug therapy (0.5-1.0 mg/kg IV) or as a lower dose (0.1-0.3 mg/kg IV) in combination with mannitol. Alterations in the blood-brain barrier do not influence the immediate or subsequent effects of furosemide on intracranial pressure. This characteristic contrasts with that of mannitol, which may produce rebound intracranial hypertension if a disrupted blood-brain barrier allows mannitol to enter the central nervous system. A combination of furosemide and mannitol is more effective in decreasing intracranial pressure than either drug alone, but severe dehydration and electrolyte imbalance are also more likely. In the presence of symptomatic hypercalcemia, furosemide may lower the plasma concentration of calcium by stimulating urine output.

Side Effects

Side effects of loop diuretics most often manifest as abnormalities of fluid and electrolyte balance. Loop diuretic use can lead to hypokalemia thus increasing the likelihood toxicity with multiple drugs including digitalis. As with thiazide diuretics, loop diuretics may cause hyperuricemia, but this is rarely clinically significant. Likewise, hyperglycemia, although possible, is less likely to occur than with thiazide diuretics.

Acute or chronic treatment of patients with diuretics, including loop diuretics, may result in tolerance to the diuretic effect ("braking phenomenon"). Acute tolerance is presumed to reflect Na and water retention (activation of the renin-angiotensin system) in the presence of contracted extracellular fluid volume.⁵ Treatment of this acute tolerance is extracellular volume repletion. With chronic use of diuretics, there is evidence of a compensatory hypertrophy of those portions of the renal tubule (especially distal convoluted

tubules) responsible for Na retention, leading to decreased diuretic effectiveness.⁵ When tolerance develops in a patient treated chronically with furosemide, it may be possible to reestablish a diuretic effect with the administration of a thiazide diuretic, to block the hypertrophied Na reabsorption sites.⁵

Loop diuretics should only be administered to patients with a normal or increased intravascular fluid volume. Acute hypovolemia may result from administration of loop diuretics to hypovolemic patients or from over treatment and the resulting hypotension may further exacerbate renal ischemic injury and concentrate nephrotoxins in the renal tubules. Accordingly, loop diuretics should be avoided in patients with acute renal insufficiency.^{2,9}

Furosemide increases renal tissue concentrations of aminoglycosides and enhances the nephrotoxicity. Cephalosporin nephrotoxicity may also be increased by furosemide. In addition, loop diuretics potentiate nondepolarizing neuromuscular blockade.² Furosemide has been associated with allergic interstitial nephritis similar to that occasionally produced by penicillin. Cross-sensitivity may exist when a patient allergic to other sulfonamides is given furosemide. The renal clearance of lithium is decreased in the presence of diuretic-induced decreases in Na reabsorption. Consequently, plasma concentrations of lithium may be acutely increased by the IV administration of furosemide in the perioperative period.

Development of ototoxicity, either transient or permanent, is a rare dose-dependent complication associated with the use of loop diuretics. This side effect is most likely to occur with prolonged increases in the plasma concentration of these drugs in the presence of other ototoxic drugs such as aminoglycosides or in the presence of chronic renal insufficiency.²

Thiazide Diuretics

Thiazide diuretics are most often administered for maintenance treatment of essential hypertension in which the combination of diuresis, natriuresis, and vasodilation are synergistic. Included in this class of drugs are hydrochlorothiazide and thiazide-like drugs, such as chlorthalidone and indapamide. Hydrochlorothiazide is the second most frequently prescribed antihypertensive medication, and thiazides are usually administered in combination with other antihypertensives.¹⁰ Also, a thiazide diuretic may be utilized to mobilize edema fluid associated with renal, hepatic, or cardiac dysfunction. Less common uses of thiazide diuretics include management of diabetes insipidus and treatment of hypocalcemia.

Pharmacokinetics and Pharmacodynamics

Thiazide diuretics produce diuresis by inhibiting reabsorption of Na and chloride ions, in the cortical portion of the ascending loop of Henle and the distal convoluted tube, by blocking the Na-chlorine cotransporter, thereby blocking 5% to 10% of the filtered Na (see [Figure 22.1](#)).² Enhanced distal delivery of Na results in increased excretion of K into the renal tubules. The result is an increase in the urinary excretion of Na, chloride, and K ions. In addition, thiazide diuretics stimulate the reabsorption of calcium in the distal convoluted tube.¹

Thiazide diuretics are readily absorbed when administered orally; hydrochlorothiazide has a 60% to 70% bioavailability.⁸ They are extensively protein bound.⁸ Most thiazides are eliminated unchanged in the kidney; indapamide, however, is metabolized by the liver.⁵ Thiazides' effectiveness is markedly reduced in patients with renal insufficiency.⁵ Thiazide diuretics have a long half-life of 8 to 12 hours, allowing for a convenient once-a-day dosing.⁸ Chlorthalidone has the longest elimination half-life of 50 to 60 hours.⁸

Indapamide, xipamide, and metolazone are structurally related to furosemide but share a thiazide-like mechanism of action with differences in their clinical effects.² Thiazide diuretics, with the exception of metolazone, are ineffective in patients with severe renal insufficiency, and the use of loop diuretics in these patients is recommended.⁸

Clinical Uses

Thiazide diuretics are recommended as first-line therapy for essential hypertension, and the use of chlorthalidone specifically has been shown to decrease the risk of major cardiovascular events when

compared to calcium channel blockers or angiotensin-converting enzyme inhibitors in a large randomized control trial, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial.¹¹

The antihypertensive effect of thiazide diuretics is due initially to a decrease in extracellular fluid volume, often with a decrease in cardiac output, which normalizes after several weeks.¹ The sustained antihypertensive effect of thiazide diuretics, however, is due to peripheral vasodilation, which requires several weeks to develop. It is unclear whether the resulting decrease in systemic vascular resistance after chronic thiazide therapy results from direct or indirect vasodilatory effect.¹⁰

Because they stimulate calcium reabsorption, thiazide diuretics are used in the treatment of calcium-containing renal calculi.¹ Although unlikely to cause hypercalcemia, thiazide diuretics should be used cautiously in patients with conditions that predispose to hypercalcemia, such as hyperparathyroidism and sarcoidosis.²

Chlorthalidone, a longer acting thiazide-like diuretic, is recommended for use in resistant hypertension, achieving better nighttime control of the blood pressure.¹ In addition, treatment with chlorthalidone resulted in decreased cardiovascular events when compared to treatment with lisinopril or amlodipine.¹¹

Indapamide, a weak diuretic, decreases blood pressure by causing vasodilation.² Xipamide on the other hand is a potent diuretic and kaliuretic, and frequent measurement of K levels are recommended.² Metolazone can promote diuresis in patients with renal insufficiency, when other thiazides are not effective, and it is usually administered with a loop diuretic. Their concomitant use should be monitored closely because of their synergism and because of metolazone's propensity to accumulate because of its prolonged elimination half-life.^{2,5,8}

Side Effects

Thiazide diuretic-induced hypokalemic, hypochloremic, or metabolic alkalosis is a common side effect when these drugs are administered chronically for maintenance treatment of essential hypertension. However, these side effects are usually tolerated at low doses.⁸ Hypokalemia may manifest as skeletal muscle weakness and gastrointestinal ileus, and it may increase the likelihood of developing digitalis toxicity. Depletion of Na and magnesium ions may accompany kaliuresis. Cardiac dysrhythmias may occur as the result of diuretic-induced hypokalemia or hypomagnesemia. In addition, hypercalcemia may result, especially in patients receiving calcium supplements or vitamin D therapy.² The use of thiazide diuretics can potentiate nondepolarizing neuromuscular blockade.² The effectiveness of thiazides is decreased in patients receiving nonsteroidal antiinflammatory drugs.⁸ In addition, thiazide diuretics may promote lithium reabsorption in the proximal tubule by a compensatory mechanism, thereby potentiating toxicity.²

Inhibition of renal tubular secretion of urate by thiazide diuretics can result in hyperuricemia in 50% of treated patients, and a small percentage of patients might develop clinical gout.^{2,10}

Thiazide diuretics may cause glucose intolerance and aggravate glucose control in diabetic patients,² especially when used in combination with β-blockers. The mechanism of hyperglycemia is unknown but may result from a drug-induced decrease of insulin release from the pancreas and peripheral resistance to the effects of insulin.¹⁰ In addition, thiazide-induced hypokalemia may be associated with glucose intolerance and treating the hypokalemia may protect from developing diabetes.⁸ Thiazide treatment may cause hyperlipidemia, affecting cholesterol and triglyceride levels.¹⁰

Intravascular fluid volume status should be considered in all patients treated with thiazide diuretics and scheduled for surgery. The presence of orthostatic hypotension in such patients should arouse suspicion that intravascular fluid volume is decreased.

Because of the structural similarities between sulfonamide antibiotics and thiazide and loop diuretics, it has been suggested that patients with sulfa allergy may demonstrate cross-reactivity to these classes of diuretics.²

Osmotic Diuretics

Osmotic diuretics such as mannitol, urea, isosorbide, and glycerin are inert substances that do not undergo metabolism and are filtered freely at the glomerulus. Their administration causes increased plasma and renal tubular fluid osmolality, with resulting osmotic diuresis.³ Portions of the renal tubules that are highly permeable to water, namely, the proximal renal tubules and more importantly, the loop of Henle, represent the principal site of action of osmotic diuretics.³

Mannitol

Mannitol is the only osmotic diuretic in current use. Structurally, mannitol is a six-carbon sugar alcohol that does not undergo metabolism. It is not absorbed from the gastrointestinal tract, which necessitates its exclusive use by IV injection to achieve a diuretic effect. Mannitol does not enter cells, and its only means of clearance from the plasma is by glomerular filtration.

Pharmacokinetics and Pharmacodynamics

After administration, mannitol is completely filtered at the glomeruli, and none of the filtered drug is subsequently reabsorbed from the renal tubules.³ By increasing tubular fluid osmolality, it decreases water reabsorption and promotes water diuresis.² The Na is diluted in this retained water in the renal tubules, leading to less reabsorption of this ion. However, hypernatremia may result from the water diuresis.²

In addition to causing renal tubular effects, IV administration of mannitol also increases plasma osmolarity, thus drawing fluid from intracellular to extracellular spaces. This increased plasma osmolarity may result in an acute expansion of the intravascular fluid volume, which could be poorly tolerated in patients with borderline cardiac function. Increased plasma osmolarity allows water to move along an osmotic gradient from tissues, including the brain, into the intravascular space, leading to decreased intracranial pressure. Mannitol is a scavenger of oxygen-free radicals, which may prevent cellular injury.

Clinical Uses

Mannitol is mainly used in the acute management of elevated intracranial pressures and in the treatment of glaucoma.

Mannitol decreases intracranial pressure by increasing plasma osmolarity, which draws water from tissues, including the brain, along an osmotic gradient. Mannitol begins to exert an effect within 10 to 15 minutes, with a peak effect at 30 to 45 minutes and a duration of 6 hours.¹² The effect on ICP is dose dependent within this dosing range, and the larger dose may last longer.¹² However, larger doses, up to 2 g/kg and repeated administration can result in metabolic derangements.¹² An intact blood–brain barrier is necessary for the cerebral effects of mannitol. If the blood–brain barrier is not intact, mannitol may enter the brain, drawing fluid with it and causing worsening of the cerebral edema.¹² In addition, a rebound increase in ICP may occur following mannitol use.¹²

Mannitol has been used to prevent perioperative kidney failure in the setting of acute tubular necrosis. It is thought to provide renal protection by several mechanisms. As an osmotic diuretic, it is not reabsorbed by the tubules and results in osmotic diuresis that forces casts and necrotic debris out of the renal tubules.¹² In addition, mannitol has been shown to cause vasodilation of vascular smooth muscle mediated by the release of prostaglandins,¹² which is dependent on the dose and rate of administration. This vasodilation leads to improved renal blood flow, thereby protecting the kidneys from acute failure following renal tubular necrosis.^{2,12} Also, mannitol has free radical scavenging properties, which could protect the transplanted kidneys following reperfusion.^{2,12} Despite its common use during cardiac and major vascular surgery for renal protection, and although mannitol increases urine output, it has not been shown to prevent perioperative acute renal failure.¹²

Side Effects

The initial increase in intravascular volume associated with the administration of mannitol may be poorly tolerated in patients with left ventricular dysfunction, leading to pulmonary edema. For this reason, furosemide may be a preferred drug for treatment of increased intracranial pressure in patients with left

ventricular dysfunction. In addition, in patients with renal insufficiency, mannitol is not filtered and will cause increase in the intravascular volume.⁵ Prolonged use of mannitol may cause hypovolemia, electrolyte disturbances with hypokalemic hypochloremia alkalosis, and plasma hyperosmolarity due to excessive excretion of water and Na.

Potassium-Sparing Diuretics

The K-sparing diuretics act on the collecting ducts and are grouped in two categories: pteridine analogues and aldosterone receptor blockers.¹ Pteridine analogues, such as triamterene and amiloride, prevent Na reabsorption in the cortical collecting duct by blocking the epithelial Na channels, independent of aldosterone. Aldosterone receptor blockers on the other hand, such as spironolactone and eplerenone, prevent the synthesis and the activation of the aldosterone-dependent basal cell Na-K-ATPase pump. Both mechanisms result in decreased Na reabsorption without the increased K secretion that would otherwise be expected.¹ The collecting duct accounts for <3% of Na reabsorption. Accordingly, K-sparing diuretics do not cause substantial diuresis and are not used as single antihypertensive therapy.^{1,13} They are used in conjunction with thiazide diuretics to prevent the associated loss of K and magnesium.⁸

Pharmacokinetics and Pharmacodynamics

Oral absorption of amiloride and triamterene is limited (25% and 50%, respectively).³ Amiloride is more potent than triamterene and is not metabolized but excreted in the kidneys.⁵ Triamterene is a pteridine with a structural resemblance to folic acid. The metabolism of triamterene by the liver is extensive, and its metabolite, secreted into the renal tubule, has diuretic activity.⁵ Accordingly, both kidney and liver disease will affect the pharmacokinetics of triamterene.⁵ The elimination half-time for triamterene is 4 hours and for amiloride is about 20 hours.³

Clinical Uses

The K-sparing diuretics are most often used in combination with loop diuretics or thiazide diuretics to augment diuresis and limit renal loss of K, and they are rarely used as monotherapy.¹³

Side Effects

Hyperkalemia is the principal side effect of therapy with K-sparing diuretics, especially when combined with angiotensin-converting enzyme inhibitor or angiotensin II receptor blockers or in presence of nonsteroidal antiinflammatory drugs (see [Table 22.1](#)).^{2,13} Although triamterene can block folic acid, it rarely causes megaloblastic anemia.¹³

Aldosterone Antagonists

Spironolactone is a synthetic steroid analogue and a nonspecific mineralocorticoid receptor antagonist.⁸ This drug bears a close structural resemblance to aldosterone and results in K-sparing diuresis. Spironolactone binds to the cytoplasmic mineralocorticoid receptors in the collecting ducts, preventing Na reabsorption via the Na-K pump. Eplerenone is a selective aldosterone receptor blocker and has less affinity for other mineralocorticoid receptors. It is, however, less potent than spironolactone.¹³ It was previously believed that spironolactone effects were solely the result of competitive antagonism of aldosterone binding to the mineralocorticoid receptors. However, it has been shown that blocking the effects of other ligands, such as cortisol, on the mineralocorticoid receptors contributes to spironolactone and eplerenone clinical effects as well.¹³ Conversely, blockade of aldosterone produces beneficial end-organ effects, independently of blood pressure control.¹³ Spironolactone, when added to conventional therapy, was shown to effectively reduce morbidity and mortality in patients with heart failure with poor ejection fraction in the Randomized Aldactone Evaluation Study.¹⁴ This is thought to be the result of prevention of aldosterone-induced cardiac remodeling and fibrosis.¹³ However, spironolactone therapy was not found to significantly improve outcomes in patients with heart failure and preserved ejection fraction (diastolic heart failure).¹⁵ Similarly, eplerenone, a selective mineralocorticoid receptor blocker, has been shown to improve morbidity and mortality compared

to optimal medical treatment in patients with acute myocardial infarction and left heart failure, in the Eplerenone in Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study.^{13,16}

Pharmacokinetics and Pharmacodynamics

Spironolactone and eplerenone exert their effect on the aldosterone receptor of the tubular cell and reach the tubular cells from the plasma and not from the tubular fluid² and are the only diuretics that do not require to reach the renal tubule to exert their effect.³ They provide competitive blockade of epithelial aldosterone receptors in the distal tubule and the collecting duct, preventing Na-K-ATPase activation and resulting in decreased Na reabsorption and in decreased K excretion.^{3,13} Oral absorption of spironolactone approaches 70% of the administered dose. Spironolactone undergoes extensive hepatic first-pass metabolism with multiple active metabolites,⁵ which account for spironolactone's long half-life of 20 hours.⁸ Spironolactone and its metabolites are extensively bound to plasma proteins and excreted by the kidneys. Similarly, eplerenone undergoes hepatic metabolism and its half-life is prolonged in the presence of CYTP3A4 inhibitors, such as ketoconazole and verapamil.¹³

Clinical Uses

Spironolactone and eplerenone are often prescribed for the treatment of essential hypertension, in combination with thiazides, particularly in patients with low renin state (such as black, elderly, and diabetic patients) or those with metabolic syndrome.¹³ Aldosterone antagonist diuretics are also used in patients with refractory hypertension, whose blood pressure remains difficult to control despite therapy with several medications, including a diuretic.¹³ Furthermore, thiazide therapy might promote increased aldosterone levels because of decreased intravascular volume.¹³ The combination of spironolactone with a thiazide diuretic results in improved diuresis and blood pressure control, in addition to prevention of the thiazide-induced hypokalemia and hypomagnesemia.⁸

In addition, spironolactone and eplerenone are indicated in the treatment of patients demonstrating "aldosterone escape." This results from incomplete aldosterone blockade during antihypertensive therapy with blockers of the renin-angiotensin-aldosterone system.^{8,13}

Aldosterone antagonists are used to promote diuresis in patients with edema and fluid overload associated with hyperaldosteronism, such as liver cirrhosis, nephrotic syndrome, and heart failure. As discussed earlier, the administration of spironolactone along with an angiotensin-converting enzyme inhibitor in the treatment of patients with heart failure with poor ejection fraction results in a decrease in cardiovascular morbidity and mortality.¹⁴

Side Effects

Hyperkalemia, especially in the presence of impaired renal function, is the most serious side effect of treatment with spironolactone. The combination of spironolactone with angiotensin-converting enzyme inhibitors can exacerbate hyperkalemia.² Because it is a nonspecific mineralocorticoid receptor antagonist, spironolactone can block androgen and progesterone receptors, leading to gynecomastia and breast tenderness⁸ that may prompt patients to seek cessation of therapy.¹⁴

Dopamine Receptor Agonists

Dopamine receptor agonists, such as dopamine and fenoldopam, result in natriuresis and increased renal blood flow, via their actions on renal tubular dopamine-1 (D₁) receptors.

Pharmacokinetics and Pharmacodynamics

Endogenous dopamine is synthesized locally in the epithelial cells of the renal tubules and exerts its effect directly.³ At low concentrations, dopamine exerts its clinical effect via activation of dopamine receptors. Activation of D₁ receptors in the proximal renal tubule and in the loop of Henle increases cyclic adenosine monophosphate formation, resulting in inhibition of the Na-H exchange and Na-K-ATPase pump.³ In

addition, D₁ receptors mediate an increase in renal blood flow leading to a small increase in glomerular filtration rate.³ With increasing doses of dopamine, sympathetic activation begins to predominate. The β activation results in increased inotropy, increased cardiac output, and elevation in systemic blood pressure. At even higher doses, α activation prevails, leading to vasoconstriction.

Fenoldopam is a fast-acting IV antihypertensive with a short half-life of 10 minutes,³ used in the short-term treatment of patients with severe hypertension. Fenoldopam is a relatively selective D₁-receptor agonist with moderate affinity to α₂ receptors. It has no effect on D₂, β, or α₁ receptors.³ Accordingly, it results in increased renal blood flow and decreased systemic vascular resistance.¹⁷ Both dopamine and fenoldopam have poor bioavailability after oral intake and are thus administered IV.

Clinical Uses

Dopamine is used to maintain renal blood flow in patients with cardiogenic shock with low or normal systemic vascular resistance.³ Similarly, fenoldopam is used for its renal vasodilation properties and because it lacks sympathetic activity, even at higher doses, it is used to treat resistant hypertension.³ Both drugs have been used at very low doses to provide renal protection in high-risk patients, such as after cardiac or major vascular surgery, or following radio contrast iodine injection.¹⁷ However, postoperative renal protection and the reduction in the incidence of perioperative acute renal failure have not been substantiated in large randomized control studies.¹⁷⁻¹⁹

Natriuretic Peptides

Atrial natriuretic peptide and brain natriuretic peptide are normally produced in the atria and ventricles of the heart, respectively, in response to myocardial wall stretch.³ They exert their diuretic effect on the collecting duct of the kidneys, by blocking the basal Na-K-ATPase channel. In the United States, nesiritide, a recombinant brain natriuretic peptide, is the only natriuretic peptide currently available. It is suggested in the management of patients with decompensated congestive heart failure,²⁰ although data on its effect on long-term morbidity and mortality are lacking.²¹ It is administered IV as a continuous infusion and has a short half-life of 18 minutes.³

Vasopressin Receptor Antagonists

Vasopressin receptor antagonists, or vaptans, competitively inhibit the V₂ receptor in the renal collecting duct, thereby leading to decreased water reabsorption. Currently, tolvaptan is the only US Food and Drug Administration-approved selective V₂ receptor antagonist for the treatment of euvolemic and hypervolemic hyponatremia associated with syndrome of inappropriate antidiuretic hormone secretion, congestive heart failure, or liver cirrhosis.²²

Pharmacokinetics and Pharmacodynamics

Tolvaptan may be orally administered in order to antagonize the effects of arginine vasopressin.²³ As a highly selective agent, it binds the V₂ receptor with an affinity 29 times stronger than that for V₁. Endogenous stimulation of the V₂ receptor by vasopressin leads to luminal translocation of the aquaporin receptor in the collecting duct.

Tolvaptan therefore blocks this action leading to enhanced aquaresis without loss of electrolytes. Onset of aquaresis occurs 2 to 4 hours after administration, with peak effect occurring within 4 to 8 hours. Tolvaptan is highly protein bound and metabolized by nonrenal routes, mainly the CYP3A system, with a half-life of about 12 hours. Moderate to severe liver impairment decreases clearance of tolvaptan, which should be avoided in patients with preexisting disease.²⁴

Clinical Uses

Tolvaptan is US Food and Drug Administration approved for the treatment of clinically significant hyponatremia, which can be seen in some patients with decompensated heart failure or syndrome of

inappropriate antidiuretic hormone secretion.³ While several studies have noted greater weight and fluid loss when tolvaptan was added to loop diuretic therapy for patients in congestive heart failure, this has not resulted in improvements in clinical measures such as symptoms, length of stay, heart failure, or postdischarge outcomes.²⁵ There have been inconsistent results regarding the improvement of dyspnea in heart failure patients treated with tolvaptan.²⁶

Side Effects

Due to Tolvaptan's ability to increase free water excretion, it is labeled with a black box warning against rapid correction of hyponatremia that could lead to potentially fatal osmotic demyelination.³ Less serious side effects include those related to polyuria, which may result in dehydration, hypotension, dizziness, pyrexia, thirst, and xerostomia. There is also potential for hyperglycemia. Treatment should be limited to 30 days due to the potential for liver damage.²⁴ Coadministration with CYP3A inducers may reduce the plasma concentration of tolvaptan, whereas CYP3A inhibitors raise the potential for toxicity.

Aquaporin Modulators

Aquaporins are recently described membrane channels that facilitate water movement across cells in response to osmotic gradient.²⁷ Subtypes of aquaporin respond to the antidiuretic hormone in the collecting duct of the kidney, and mutations in those channels can result in hereditary nephrogenic diabetes insipidus.^{2,27} Other subunits located in the cerebral perivascular astrocyte end foot may be involved in cerebral edema and in the pathogenesis of neuromyelitis optica.^{2,27} Nephrogenic diabetes insipidus (NDI), which is characterized by polyuria and polydypsia, results from an inappropriate response to the antidiuretic hormone. The most common form of NDI is acquired, usually secondary to lithium toxicity, hypercalcemia, or polycystic kidney disease. Hereditary NDI on the other hand is rare and can result either from an X-linked defect in V₂ receptors or from an autosomal recessive AQP2 mutation.²⁷ Treatment with thiazide diuretics in these patients helps decrease the kidney's diluting ability.²⁷

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Lipid-Lowering Drugs*

Updated by: Peter C. Schmidt

Lipoprotein Metabolism

Lipoproteins are macromolecular lipid protein complexes responsible for the transport of lipids to and from the peripheral tissues. Lipoproteins are classified based on their relative density as (1) chylomicrons, (2) very low-density lipoproteins (VLDLs), (3) intermediate-density lipoproteins, (4) low-density lipoproteins (LDLs), and (5) high-density lipoproteins (HDLs) ([Table 23.1](#)). Lipoprotein metabolism can be divided into the exogenous and endogenous pathways ([Figure 23.1](#)). The exogenous pathway refers to the processing of dietary fats, cholesterol, and lipid-soluble vitamins, whereas the endogenous pathway describes hepatic cholesterol synthesis and its distribution to the peripheral tissues.

TABLE 23.1

Classification of lipoproteins

Lipoprotein	Density (g/mL)	Diameter (nm)
Chylomicrons	<0.95	75-1,200
Very low-density lipoproteins	0.95-1.006	30-90
Intermediate-density lipoproteins	1.006-1.019	~30
Low-density lipoproteins	1.019-1.063	~20
High-density lipoproteins	1.063-1.21	8-12

From Jackson RL, Morrisett JD, Gotto AM Jr, et al. Lipoprotein structure and metabolism. *Physiol Rev.* 1976;56(2):259-316; Mahley RW, Innerarity TL, Rall SC Jr, et al. Plasma lipoproteins: apolipoprotein structure and function. *J Lipid Res.* 1984;25(12):1277-1294.

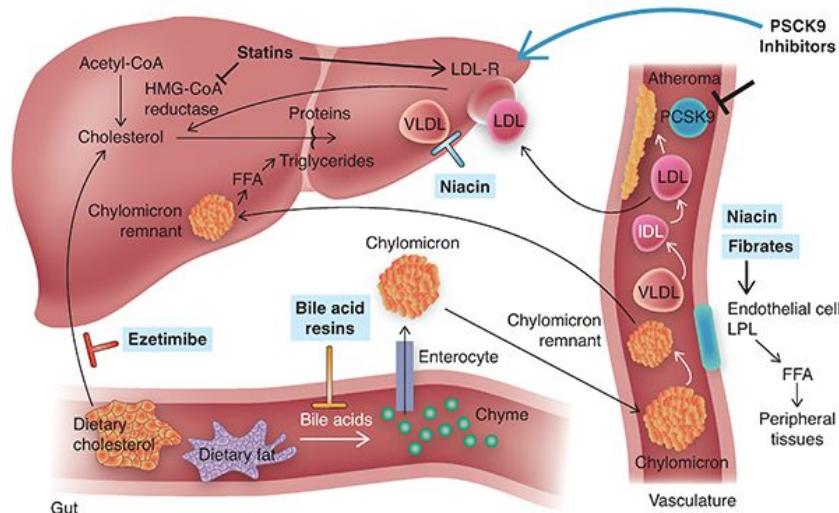


FIGURE 23.1 A diagrammatic representation of lipid metabolism. T-shaped markers indicate inhibition, and arrow-shaped markers indicate enhancement. Abbreviations: FFA, free fatty acid; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LDL-R, low-density lipoprotein receptors; LPL, lipoprotein lipase; PCSK9, proprotein convertase subtilisin/kexin type 9; VLDL, very low-density lipoprotein.

Exogenous Pathway

In the small intestine, bile emulsifies dietary fat and cholesterol, and lipase excreted by the pancreas hydrolyzes triglycerides. The intestinal endothelium takes up these products by endocytosis and packages lipids into large chylomicrons, which then enter the lymphatic system. After traveling through the thoracic duct, the chylomicrons enter the bloodstream where they interact with lipoprotein lipase in vascular endothelial cells, yielding glycerol and free fatty acids, which can be used by the peripheral tissues for fuel or storage. During this process, the chylomicrons shrink and become chylomicron remnants. These remnants are transported to the liver where they are taken up by hepatocytes via endocytosis and subsequently hydrolyzed.

Endogenous Pathway

In the liver, hepatocytes synthesize cholesterol, lipids, and proteins, which are assembled into VLDL and excreted into the bloodstream. Similar to the processing of chylomicrons, endothelial cell lipoprotein lipase hydrolyzes the fats in VLDL particles, which then shrink to form intermediate-density lipoprotein and LDL. The LDL particles contain most of the cholesterol in plasma and are cleared from the blood by binding to LDL receptors (LDL-R) on hepatocytes. Apolipoproteins C and E are essential cofactors of the hydrolysis of VLDL and are contributed by HDL particles. The HDL also transfers apolipoprotein C2 to chylomicrons in the exogenous pathway and is responsible for reverse cholesterol transport, in which excess cholesterol is delivered from the peripheral tissues to the liver for excretion in the bile.¹

Lipid Disorders

A minority of lipid disorders arise from genetic defects in lipoprotein metabolism, which may present in the pediatric period or early adulthood. One such disorder, familial hypercholesterolemia, arises from a defect in the gene for LDL-R. Heterozygotes for this defect experience accelerated atherosclerosis and represent about 1 in 500 persons. Homozygotes are much rarer, have total and LDL cholesterol levels 4 times normal, and have an extreme propensity for atherosclerosis. Hyperlipidemia may also arise from secondary causes including obesity, diabetes, alcohol abuse, hypothyroidism, glucocorticoid excess, and hepatic or renal dysfunction.¹ Most cases of hyperlipidemia in adults arise from a combination of secondary causes, genetic predisposition, and environmental factors, including poor diet and a lack of exercise.²

It has been recognized for several decades that increased plasma concentrations of total and LDL cholesterol are associated with an increased risk of cardiovascular disease.^{3,4} Conversely, higher HDL cholesterol levels appear to reduce the risk of atherosclerosis and cardiovascular events because of the critical role of HDL in reverse cholesterol transport.⁵⁻⁷ Furthermore, lowering plasma concentrations of total and LDL cholesterol with pharmacologic agents decreases the risk of coronary events in patients with and without coronary artery disease.^{8,9} Hypertriglyceridemia is known to cause pancreatitis, but its causal relationship to atherosclerosis is less well established.²

The safety and efficacy of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or statins, have been particularly well established and have become the mainstay of treatment of hyperlipidemia,^{9,10} as reflected in current guidelines issued by the American College of Cardiology and the American Heart Association. These guidelines advocate statin use in five risk-stratified groups (**Table 23.2**) for the primary or secondary prevention of atherosclerotic cardiovascular disease and in other groups dependent on the presence of associated risk factors. In fact, American College of Cardiology and the American Heart Association guidelines no longer recommend the use of drugs other than statins for the treatment of hyperlipidemia.¹¹ Based on these guidelines, well over 50 million adults in the United States are eligible for statin therapy.¹² Therefore, anesthesiologists can expect to routinely encounter patients taking statins in the perioperative period. However, alternative agents to statins are still used in clinical practice for the treatment of familial lipid disorders, for those with very high LDL levels, and for those who are intolerant of statins.

TABLE 23.2

Statin benefit groups

1. Clinical evidence of ASCVD

2. LDL-C \geq 190 mg/dL
3. Age 40-75 years with diabetes mellitus
4. Age 40-75 years without diabetes, an LDL-C 70-189 mg/dL, and an estimated 10-year risk of ASCVD >5% to <20% and risk enhancers favor statin
5. Age 40-75 years without diabetes, an LDL-C 70-189 mg/dL, and an estimated 10-year risk of ASCVD \geq 20%^a

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol.

^a10-year risk of ASCVD based on pooled cohort equations available at my.americanheart.org/cvriskcalculator.

Adapted from Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2019;74(10):1376-1414.

Drugs for Treatment of Hyperlipidemia

Statins have become the mainstay of and sole agents recommended for the treatment of hyperlipidemia; however, there are multiple other agents still used for patients intolerant of statins or those with genetic lipid disorders. The effects of these different classes of medications on LDL, HDL, and triglycerides are summarized in [Table 23.3](#).

TABLE 23.3

Drugs for treatment of hyperlipidemia

	LDL	HDL	Triglycerides
Diet change	↓ 10%-15%	Variable increase	↓ 10%-20%
Statins	↓ 20%-60%	↑ 5%-10%	↓ 10%-20%
Bile acid resins	↓ 15%-30%	↑ 3%-5%	No change or mild increase
Fibrates	↓ 5%-20% or increase	↑ 10%-35%	↓ 40%-50%
Ezetimibe	↓ 18%	↑ 1%	↓ 8%
Niacin	↓ 15%-30%	↑ 20%-30%	↓ 20%-50%
PCSK9 inhibitors	↓ 38%-72%	↑ 4%-9%	↑ 2%-23%

Abbreviations: ↑, increase; ↓, decrease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PCSK9, proprotein convertase subtilisin/kexin type 9.

Statins

Statins act as inhibitors of HMG-CoA reductase, the enzyme that catalyzes the rate-limiting step of cholesterol biosynthesis in which HMG-CoA is converted to mevalonate (see [Figure 23.1](#)). Statins are structurally related to HMG-CoA, and competitive inhibition of the enzyme causes an increase in hepatic LDL-R. The combined effect of decreased cholesterol synthesis and increased LDL uptake by the liver by statins results in a decrease in LDL concentration of 20% to 60%. Statins also increase HDL by approximately 10%, possibly from increased synthesis of apolipoprotein A1. Plasma triglyceride concentrations decrease 10% to 20% in statin-treated patients, although this is usually insufficient as the sole treatment of hypertriglyceridemia.²

The drugs in this class (atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin, pitavastatin and rosuvastatin) are considered largely equivalent. Randomized clinical trials have shown that statins lower cardiac events (total mortality, death from myocardial infarction, revascularization procedures, stroke, and peripheral vascular disease) in patients with or without atherosclerosis.^{13,14} Furthermore, angiographic studies have shown benefit on coronary stenosis in native vessels or grafts in patients treated with statins as

well as in patients experiencing acute coronary syndromes.¹⁵ Early initiation of statin therapy following an acute myocardial infarction is recommended.^{16,17}

The reduction in cardiac events observed with statin use may not be solely due to LDL-lowering effects. Statins are thought to stabilize existing atherosclerotic plaques, and there is evidence that statins have many pleiotropic effects, including antiinflammatory, antioxidant, and vasodilatory properties. Reduced perioperative morbidity and mortality has even been reported in observational studies following perioperative statin administration, although this is not yet widely advocated.¹⁸

Pharmacokinetics

Statins are variably absorbed from the gastrointestinal tract following oral ingestion. Bile acid–binding resins can decrease the absorption of these drugs. Lovastatin and simvastatin are prodrugs that require metabolism to the open β -hydroxy acid form to be pharmacologically active. Food intake increases plasma concentrations of lovastatin but has minimal effects on the other statins. All of the statins are highly protein bound with the exception of pravastatin. Also with the exception of pravastatin, all of the statins undergo extensive metabolism by hepatic P450 enzymes. Elimination half-times vary widely, from 30 minutes to 30 hours, depending on drug and formulation (immediate release vs extended release).

Despite the short elimination half-times, the duration of pharmacodynamic effects is about 24 hours. This is a consideration in the perioperative period when patients may not be able to ingest oral medications. Atorvastatin and fluvastatin undergo minimal renal excretion and likely do not require dosage adjustments in patients with renal insufficiency. Statins are teratogenic in animals and thus are not recommended for use during pregnancy.¹⁹

Side Effects

Statins are generally well-tolerated, with common complaints being gastrointestinal upset, fatigue, and headache. A meta-analysis of 22 placebo-controlled statin trials revealed slightly more subjects discontinued dosing in the placebo groups (13.9%) than in the active groups (13.3%) over a mean duration of 4.1 years.²⁰ In clinical trials, less than 5% of patients treated with statins experienced adverse effects, similar to the rates in placebo-treated groups. However, in clinical practice, there are several side effects of concern, most notably muscle-related effects and liver abnormalities.

Muscle-Related Side Effects

The most common adverse events requiring discontinuation or switching of statins in clinical practice are skeletal muscle related. Statin-associated muscle symptoms can range in severity from simple myalgias to myositis with mild creatine kinase elevation to life-threatening rhabdomyolysis characterized by a greater than 10-fold elevation in creatine kinase. Myositis and rhabdomyolysis are quite rare and in clinical trials occur with similar frequency in placebo-treated groups. Conversely, myalgias are reported in as many as a third of statin-treated patients in clinical practice and more commonly in patients with certain risk factors (**Table 23.4**).²¹ The mechanisms underlying statin-related myotoxicity are incompletely understood. It is possible that by inhibiting HMG-CoA reductase, statins decrease not only cholesterol synthesis but also the formation of ubiquinone (otherwise known as coenzyme Q10), which is important for mitochondrial function and cell membrane integrity.²² Alternatively, decreased cholesterol levels in skeletal muscle cell membranes may increase membrane fluidity, leading to unstable sarcolemma, myotonic discharges, and, in advanced but rare situations, rhabdomyolysis.²³

TABLE 23.4

Statin myotoxicity risk factors

- Age >80 years
- Female sex
- Very low vitamin D
- Asian ethnicity
- Renal/hepatic failure

Low body mass index, small frame
Preexisting neuromuscular or muscular disorders
Diabetes mellitus
Certain genetic polymorphisms
Poorly controlled hypothyroidism

Adapted from Mancini GB, Baker S, Bergeron J, et al. Diagnosis, prevention, and management of statin adverse effects and intolerance: Canadian Consensus Working Group update (2016). *Can J Cardiol.* 2016;32(7 suppl):S35-S65.

Severe muscle-related adverse events associated with statin use are often secondary to drug interactions with agents that are also metabolized by the hepatocyte cytochrome P450 (CYP) system. Myopathy appears to be most frequent in patients treated with atorvastatin, simvastatin, and lovastatin, as these are metabolized by CYP3A4 and their concentrations are increased by CYP3A4 inhibitors, including warfarin, protease inhibitors, macrolide antibiotics, and azole antifungals. Fluvastatin, pravastatin, and pitavastatin have the lowest rate of events. Drugs likely to be administered during anesthesia, including succinylcholine, have not been shown to increase the incidence of statin-induced myopathy.²²⁻²⁴

Hepatic Dysfunction

Persistent increases in plasma aminotransferase concentrations occur in 0.5% to 3% of treated patients and are dose-dependent. This commonly manifests during the first 3 months of therapy. Discontinuation of the drug is recommended if plasma aminotransferase concentrations increase to more than 3 times normal. Progression to hepatic failure is extremely rare.²

Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors

Two proprotein convertase subtilisin/kexin type 9 (PCSK9) antibodies are currently available: evolocumab and alirocumab. Both act by binding PCSK9 in the blood, leading to increased hepatic expression of LDL-R and increased clearance of LDL from the blood.^{25,26}

Evolocumab is indicated for the reduction of myocardial infarction, stroke, and coronary artery revascularization in adults with existing cardiovascular disease, and as an adjunct to diet, alone or in combination with other lipid-lowering therapies, for treatment of adults with primary hyperlipidemia. It is also indicated for the treatment of patients with homozygous familial hypercholesterolemia.

Alirocumab carries a similar indication and includes the treatment of heterozygous familial hypercholesterolemia.

Pharmacokinetics

Both drugs are administered subcutaneously, every 2 weeks. Evolocumab can also be administered monthly with a higher dose. Maximum suppression of PCSK9 occurs between 4 to 8 hours after injection. As these drugs are proteins, elimination is through target binding and proteolysis. Evolocumab has a half-life of 11 to 17 days and alirocumab has a slightly longer half-life of 17 to 20 days. The half-lives of both drugs are prolonged with the coadministration of a statin, but this is not to be considered clinically relevant.

Side Effects

The PCSK9 inhibitors are generally well tolerated, with the most common adverse events being upper respiratory tract infections, influenza, and injection site reactions.

Bile Acid Resins

Bile acid resins may be effective for the treatment of lipid disorders in which the primary abnormality is an increased plasma LDL cholesterol concentration with a normal or near-normal triglyceride level. The three drugs in this class, colestevam, cholestyramine, and colestipol, have a low potential for toxicity, but gastrointestinal side effects are often dose-limiting. There is no systemic absorption of these resins.

Administered as monotherapy, bile acid-binding resins decrease plasma concentrations of LDL cholesterol

by 15% to 30%. Plasma concentrations of triglycerides may increase 5% to 20% in treated patients owing to increased production of VLDLs.

Bile acid resins bind bile in the intestine, interrupting enterohepatic circulation and increasing fecal excretion that increases hepatic bile acid synthesis from cholesterol stores (see [Figure 23.1](#)). This increases the production of hepatic LDL-R and increases the uptake of LDL cholesterol from blood, lowering plasma concentrations of LDL cholesterol. The HMG-CoA reductase activity also increases.

Side Effects

Palatability and constipation are common complaints in patients being treated with cholestyramine. A high fluid intake is useful in minimizing constipation. Colesevelam has fewer gastrointestinal side effects and is approved for use in adolescents with familial hypercholesterolemia. There may be transient increases in the plasma concentrations of alkaline phosphatase and transaminases.

Because cholestyramine is a chloride form of an ion exchange resin, hyperchloremic acidosis can occur, especially in younger and smaller patients in whom the relative dose is larger. Absorption of fat-soluble vitamins as well as other pharmacologic agents may be impaired. For this reason, other drugs should be given at least 1 hour before or 4 hours after administration of cholestyramine.

Niacin

Niacin (nicotinic acid) is a water-soluble B complex vitamin that inhibits synthesis of VLDLs in the liver by an unknown mechanism (see [Figure 23.1](#)). In addition, niacin inhibits release of free fatty acids from adipose tissue and increases the activity of lipoprotein lipase. The result of these effects is a dose-related 15% to 30% decrease in plasma LDL cholesterol concentrations, a 20% to 50% decrease in triglycerides, and a 20% to 30% increase in HDL. Niacin does not produce any detectable changes in synthesis of cholesterol, nor does it alter excretion of bile acids.²⁷

Pharmacokinetics

Niacin is readily absorbed from the gastrointestinal tract and undergoes extensive hepatic first-pass metabolism. The primary route of metabolism is methylation to *N*-methyl-nicotinamide. Niacin also undergoes conjugation with glycine to produce nicotinuric acid. Metabolites undergo renal excretion and at high doses, niacin undergoes renal excretion unchanged.

Side Effects

Niacin is often poorly tolerated, which may limit its usefulness. The most common side effect is intense prostaglandin-induced cutaneous flushing that occurs in about 10% of patients. Aspirin administered 30 minutes before ingestion of niacin decreases flushing, whereas alcohol ingestion potentiates flushing. Abdominal pain, nausea and vomiting, diarrhea, and malaise are common complaints in treated patients. Hepatic dysfunction manifesting as increased plasma transaminase activity and cholestatic jaundice may be associated with large doses of niacin. Therefore, niacin is not recommended for administration to patients with liver disease. Hyperglycemia and abnormal glucose tolerance may occur in nondiabetic patients treated with niacin. Plasma concentrations of uric acid are increased, increasing the incidence of gouty arthritis. Niacin may exaggerate the orthostatic hypotension associated with antihypertensive drugs and the myopathy associated with statins. Peptic ulcer disease may be reactivated by niacin.

Fibrates

Fibrates are derivatives of fibric acid and are effective drugs for decreasing plasma concentrations of triglycerides. In the postoperative period, treatment with fibrates is restarted when the patient is well hydrated and able to ingest oral medications. There are three fibric acid derivatives commonly used for the treatment of hyperlipidemia: gemfibrozil, fenofibrate, and bezafibrate. Clofibrate was the original fibric acid derivative for treatment of increased plasma triglyceride concentrations. This drug is no longer considered the drug of choice, principally because of concern that noncardiovascular adverse events may be increased in treated patients.²⁸ Fibrates produce a dose dependent 40% to 50% decrease in plasma triglycerides and 10% to 35%

increase in HDL concentrations, whereas the effect on LDL concentrations is variable. Drug-induced increase in the activity of lipoprotein lipase is the likely mechanism for the triglyceride-lowering effects of these drugs (see [Figure 23.1](#)). This action of fibrates may reflect activation of specific transcription factors (peroxisome proliferator-activated receptors), which result in upregulation of genes for lipoprotein lipase and fatty acid oxidation. Induction of lipoprotein lipase contributes to lipolysis of triglyceride-rich lipoproteins, VLDL, and chylomicrons. When the LDL concentration increases, it is presumed to reflect improved catabolism of VLDLs and, hence, increased production of LDLs. Bezafibrate is also thought to improve insulin sensitivity.²⁹

Pharmacokinetics

Gemfibrozil is well absorbed from the gastrointestinal tract following oral administration. Metabolism is by oxidation of a methyl group to form a hydroxymethyl and then a carboxyl metabolite. Protein binding is extensive. The elimination half-time of gemfibrozil is approximately 15 hours, with an estimated 70% of a single dose appearing unchanged in the urine. Fenofibrate is a prodrug that is hydrolyzed by esterases to the active metabolite, fenofibric acid. Fenofibric acid is metabolized by conjugation with glucuronic acid that undergoes extensive renal excretion. The elimination half-time of fenofibrate is about 20 hours. Absorption of fenofibrate is increased when the drug is administered with food. Protein binding is approximately 99%. Increased plasma concentrations of liver transaminase enzymes are more likely to occur with fenofibrate than with the other fibrates.

Side Effects

The most common side effects of the fibrates are gastrointestinal (abdominal pain, nausea) and headache. Gemfibrozil increases the cholesterol content of bile (lithogenicity) and may increase the formation of gallstones. The incidence of skeletal muscle myopathy and risk of rhabdomyolysis is increased when this drug is administered in combination with statins, especially lovastatin. The anticoagulant effect of warfarin is potentiated by gemfibrozil, presumably reflecting its displacement from binding sites on albumin. A mild increase in plasma transaminase enzymes may occur in treated patients. Considering the dependence on renal excretion for elimination and occasional increases in liver function tests, it may be prudent to avoid administration of this drug to patients with preexisting renal or hepatic disease. The increase in noncardiovascular mortality observed with clofibrate²⁸ may be due to low plasma cholesterol concentrations, which predispose patients to hemorrhagic stroke, particularly when systemic hypertension is present.³⁰

Ezetimibe

Ezetimibe acts as a selective inhibitor of cholesterol absorption, which leads to a secondary upregulation of LDL-R (see [Figure 23.1](#)). Cholesterol absorption is inhibited because of ezetimibe's ability to disrupt a complex between the annexin-2 and caveolin-1 proteins in the brush border of the small intestine. Used as monotherapy, ezetimibe decreases LDL cholesterol levels by 8% to 22%, and it can potentiate the effect of statins by an additional 17%. It modestly influences triglyceride levels and has a negligible effect on HDL cholesterol levels.²⁷ Clinical trials addressing the efficacy of ezetimibe in improving cardiovascular endpoints have been conflicting, with some showing a decreased risk of atherosclerotic events when used in conjunction with statins, whereas others have had negative results.^{31,32} It may be helpful in avoiding high-dose statin therapy.

Side Effects

Ezetimibe is very well tolerated, with adverse event rates similar to placebo in clinical trials.

Omega-3 Fatty Acids (Fish Oil)

One type of fat present in marine fish oils is highly unsaturated omega-3 fatty acid. The primary effect of this fatty acid is to decrease plasma concentrations of triglycerides, whereas the effect on the plasma LDL cholesterol concentrations is variable. It is not clear what dose is necessary to cause desirable effects on the plasma concentrations of triglycerides. Fish oil supplements are not regarded as drugs and thus are not

regulated by the U.S. Food and Drug Administration. The long-term safety of taking fish oil capsules is not known, and there is no evidence that fish oil supplementation prevents heart disease. The use of this supplement is of primary concern to the anesthesiologist due to the increased risk of bleeding.³³

Other Agents

Lomitapide is an inhibitor of microsomal triglyceride transfer protein, an intracellular lipid transport protein that is thought to be important for the production of chylomicrons in the intestine and VLDL by hepatocytes. It is indicated for homozygous familial hypercholesterolemia and carries a boxed warning for risk of hepatotoxicity and is only available through a restricted-access program.³⁴

Mipomersen is an oligonucleotide inhibitor of apolipoprotein B100 that is similarly approved for the treatment of patients with homozygous familial hyperlipidemia. Like lomitapide, mipomersen frequently causes elevations in liver enzymes as well as steatosis and is subject to a boxed warning and a restricted access program. It is not currently being marketed in the United States.³⁵

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*The sixth edition authors gratefully acknowledge the past updates by the previous edition authors, Sarah C. Smith and Jack S. Shanewise, as portions of that chapter were retained in this revision.

PART IV Pulmonary System

Gas Exchange

Alexander Huang • Peter Slinger

*The essentials of anesthesia are applied physiology,
pharmacology, and clinical monitoring
with a little bit of internal medicine.*

John Sandison, 1980

*Respiratory physiology is difficult; if the answer
is simple you don't understand the question.*

Peter Slinger, 2013

During surgery, the anesthesiologist becomes, in part, an applied respiratory physiologist, and an understanding of the physiology and pharmacology pertaining to the respiratory system is fundamental to anesthetic management. Understanding gas exchange is particularly challenging because respiratory physiology is not an exact science. Anesthesiologists work mainly with concepts that allow them to treat and predict the alterations in respiration associated with anesthesia and a variety of diseases. However, these concepts are all specific to the context of a patient's gas exchange at a specific time and in a specific situation and often cannot be extrapolated precisely to a situation of altered physiology. As discussed, even fundamental basics of respiratory physiology such as **dead space** and **functional residual capacity** (FRC) are never absolute values but are dynamic and always changing.

Functional Anatomy

Upper Airway Anatomy and Gas Flow

Oropharynx and Nasopharynx

The air passages extending from the nares and lips through the nasopharynx and oropharynx, through the larynx to the cricoid cartilage make up the functional upper airway. The upper airway serves a host of functions: warming and humidifying passing air, filtering particulate matter, and preventing aspiration.¹

During normal quiet breathing, air enters via the nose, a chamber separated in the midline along its entire length by a cartilaginous and bony septum. It is bounded laterally by the inferior, middle, and superior turbinates overlying the sinus ostia and inferiorly by the hard and soft palates and joining the nasopharynx posteriorly. The mucosa covering these structures is highly vascular and well innervated, facts that must be appreciated when performing nasopharyngeal intubation with endotracheal tubes, nasogastric sumps or feeding tubes, or fiberoptic bronchoscopes. This tissue is sensitive to even modest stimulation and is easily torn, leading to significant bleeding. The nasal passages represent a significant resistance to airflow, normally double that found in mouth breathing. Hence, normal subjects or patients will revert to mouth breathing during exercise or respiratory failure.

The pharynx is 12 to 15 cm long and is divided into the nasopharynx, the oropharynx, and the laryngopharynx (lying posterior to the larynx). The oropharynx is further subdivided into the velopharynx (posterior to the soft palate) and the retroglossal pharynx (posterior to the base of the tongue) ([Figure 24.1](#)).² The supine position, sleep, and general anesthesia may promote obstruction of the oropharynx by the tongue, soft palate, and pharyngeal musculature as their tone decreases.³ Flexion of the cervical spine generally increases upper airway resistance. During inspiration, a nonsedated, spontaneously breathing patient dilates

the oropharyngeal pharynx by contracting the genioglossus muscle and elevating the tongue off the pharyngeal wall in a coordinated reflex. This subconscious phasic inspiratory dilation opposes the tendency of the upper airway to collapse due to the negative airway pressure generated by the diaphragm during inspiration. Unfortunately, this reflex genioglossus activity is easily abolished by low doses of most anesthetics, with the exception of ketamine.⁴

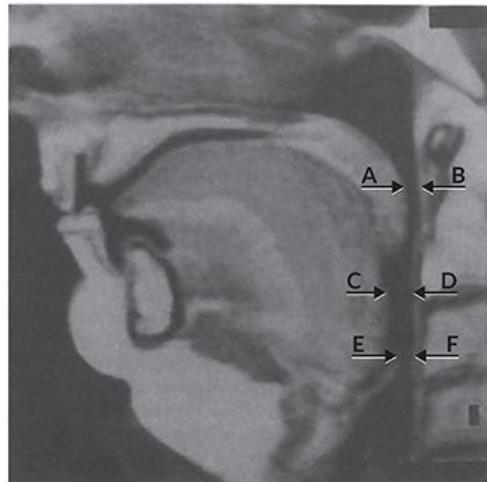


FIGURE 24.1 Sagittal magnetic resonance imaging of the upper airway of an awake patient. A-B is the junction of nasopharynx with velopharynx, C-D is the retroglossal pharynx, and E-F is the minimum anteroposterior upper airway diameter at the tip of the epiglottis. The laryngopharynx extends downward from E-F to the cricoid cartilage. *Reprinted with permission from Shorten GD, Opie NJ, Graziotti P, et al. Assessment of upper airway anatomy in awake, sedated and anaesthetised patients using magnetic resonance imaging. Anaesth Intensive Care. 1994;22(2):165-169. Copyright © 1994 SAGE Publications.*

Larynx

The larynx is a complex structure that lies anterior to the 4th to the 6th cervical vertebrae and consists of several muscles, their ligaments, and associated cartilaginous structures (**Figure 24.2**). The inlet of the larynx is bordered by the epiglottis, aryepiglottic folds, and the arytenoids. The larynx itself bulges into the pharynx posteriorly creating a deep pharyngeal recess anterolaterally on either side, the pyriform fossae. The pyriform fossae, which lie to each side of midline, are clinically relevant because of their tendency to trap food or foreign objects in the pharynx and as potential sites for the application of topical anesthesia to block the internal branch of the superior laryngeal nerve. The larynx serves as the organ of phonation and plays an important role in coughing and in protection of the airway from entrainment of solids and liquids during swallowing.⁵

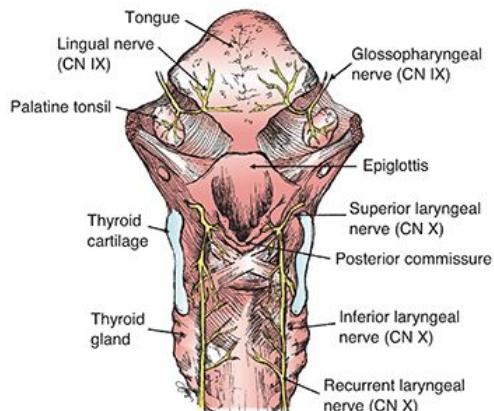


FIGURE 24.2 Diagram of the larynx from the base of the tongue to below the thyroid cartilage as viewed from its posterior aspect. Note the relationship of the superior laryngeal, inferior laryngeal, and recurrent laryngeal nerves and the posterior aspect of the larynx, thyroid, and trachea. Tracheal and thyroid surgery places these nerves at risk. *Reprinted by permission from Springer: Jaeger JM, Blank RS. Essential anatomy and physiology of the respiratory system and the pulmonary circulation. In: Slinger P, ed. Principles and Practice of Anesthesia for Thoracic Surgery. New York, NY: Springer; 2011:51-69. Figure 4.1. Copyright © 2011 Springer Science+Business Media, LLC.*

The primary support structure of the larynx is the thyroid cartilage that forms the point of articulation of the paired arytenoid cartilages with the vocal ligaments and their controlling musculature. Other essential structures include the hyoid bone and its attachments, the epiglottis, the cricoid cartilage, and the corniculate cartilages. The hyoid bone is a U-shaped bone that is attached directly to the stylohyoid ligament and muscle; to the mandible and tongue by the hyoglossus, mylohyoid, geniohyoid, and digastric muscles; and to the pharynx by the middle pharyngeal constrictor muscle. Beneath the hyoid bone is the remainder of the larynx suspended by its attachment, the thyrohyoid membrane and muscle. Although its function other than as a flexible anchor is unclear, it is possible to bisect its mandibular attachments (“suprathyroid release”) and mobilize the larynx in order to facilitate its caudal displacement in tracheal resection procedures. The epiglottis is the midline elastic cartilage found inferior to the base of the tongue. It is anchored anteriorly to the hyoid bone and inferiorly to the inside of the anterior portion of the thyroid cartilage immediately above the vocal cords. Bilateral folds of the epiglottis curve posteriorly to form a mucosal ridge attached to the arytenoid cartilages sitting on top of the posterior lamina of the cricoid, the aryepiglottic folds. The epiglottis, aryepiglottic folds, and the corniculate tubercles form the inlet into the glottis below. The thyroid cartilage contains the larynx with its paired lamina fused anteriorly at the laryngeal prominence and extending posteriorly to terminate in superior and inferior horns or cornu. The thyroid cartilage serves as a stable point of attachment for numerous small muscles and ligaments, which manipulate the vocal cords. The thyroid cartilage also has a mobile, membranous attachment to the cricoid ring.

The paired vocal cords attach posteriorly to the vocal process of each arytenoid and anteriorly meet at the junction of the thyroepiglottic ligament of the anterior portion of the thyroid cartilage. The triangular opening formed by the vocal ligaments is the glottis with its apex anteriorly (**Figure 24.3**). The mean length of the relaxed open glottis is approximately 23 mm in males and 17 mm in females. The glottis at its widest (posterior) point is 6 to 9 mm but can be “stretched” to 12 mm.⁶ It should be noted that the vocal cords are covered by a thin, adherent mucosa, producing a pearly white appearance. The absence of any submucosa implies that the vocal cords are unlikely to “swell” significantly as there is minimal space to accumulate edema fluid. However, the folds of mucosa and fibrous tissue lying parallel to the true vocal cords just superiorly in the glottis, the vestibular folds or “false vocal cords,” can become edematous. The intrinsic laryngeal musculature functions to open the glottis during inspiration; close the glottis and constrict the superior structures during swallowing; and finely control abduction, adduction, and tension of the true vocal cords during phonation.

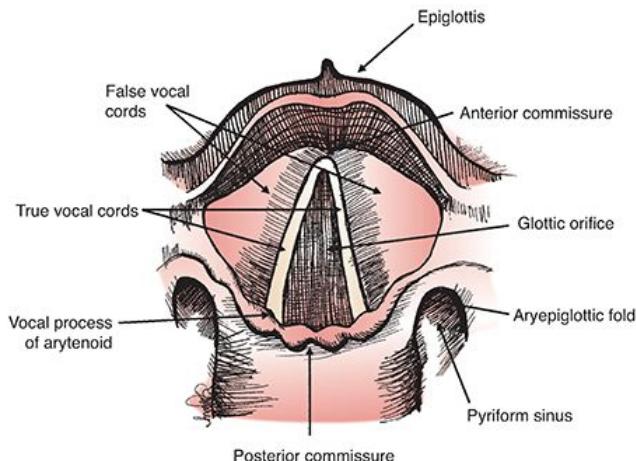


FIGURE 24.3 Diagram of the glottis as seen from above using a laryngoscope or fiberoptic bronchoscope. Note the triangular-shaped glottic introitus with its narrowest aspect at the anterior commissure. Passage of bronchoscopes, endotracheal tubes, and, especially, double-lumen tubes should be directed posteriorly where the vocal cords will spread the widest. Note that the vocal process of the arytenoid cartilage pivots on a small point and can be traumatized and displaced with rough handling. *Reprinted by permission from Springer: Jaeger JM, Blank RS. Essential anatomy and physiology of the respiratory system and the pulmonary circulation. In: Slinger P, ed. Principles and Practice of Anesthesia for Thoracic Surgery. New York, NY: Springer; 2011:51-69. Figure 4.2. Copyright © 2011 Springer Science+Business Media, LLC.*

Pharyngeal Innervation

Innervation of the pharynx is supplied via sensory and motor branches of the glossopharyngeal nerve (CN IX) and vagus nerve (CN X) (external and internal branches of the superior laryngeal nerves, recurrent laryngeal nerves). The sensory innervation of the nasopharynx is derived from the maxillary division of the trigeminal nerve (CN V), whereas the oropharynx is diffusely innervated by sensory branches from the glossopharyngeal nerve (CN IX). The internal branch of the superior laryngeal nerve pierces the lateral aspect of the thyrohyoid membrane along with the superior laryngeal artery and vein to provide sensation for the base of the tongue, vallecula, epiglottis, aryepiglottic folds, pyriform recesses, and the superior aspect of the true vocal cords. The external branch of the superior laryngeal nerve provides motor innervation to the cricothyroid muscle, a tensor of the true vocal cords. The recurrent laryngeal nerves supply sensation to the vocal cords and tracheobronchial tree as well as motor innervation to all the remaining intrinsic musculature of the larynx. The right recurrent laryngeal nerve passes inferior to the right subclavian artery, but the left originates at the level of the aortic arch and loops around the ligamentum arteriosum then both nerves ascend cephalad along the tracheoesophageal groove. This anatomy must be appreciated during esophageal and thyroid surgery and during both cervical and anterior mediastinoscopy, as these structures can be at risk. The larynx receives its blood supply from the superior and inferior laryngeal arterial branches of the superior and inferior thyroid arteries, respectively. These arteries follow the course of the superior and recurrent laryngeal nerves.

The major function of the upper airway is to provide a conduit for the initial inhalation then exhalation of gases to and from the lungs while contributing to multiple other functions (eg, eating, drinking, speaking). With respect to inhalation, the nasopharynx and posterior pharynx warm and humidify the inspired gas. This aids in maintaining core temperature and protects the more delicate epithelial lining of the lower airways from desiccation. The airway epithelium secretes mucus, which coats the airway surface and maintains tissue hydration and also serves to trap particulate matter, bacteria, and viruses. Mucus also contains a number of enzymes with antioxidant, antiprotease, and antibacterial properties.⁷

Another important role of the airways and their mucus coat is the filtering of inhaled particulate matter by an elaborate defense system that takes advantage of the airflow characteristics of the upper and lower

airways and their associated epithelium. There are three mechanisms at work to produce mechanical filtering of inspired gases.¹ The first, inertial impaction, is capable of trapping particles larger than 10 microns by virtue of the turbulent flow across the mucus lining of the passageways. It accomplishes this task in minutes with mucus and saliva eventually swallowed. Gas flow slows within the bifurcating and branching tracheobronchial tree until it becomes more laminar. Particulates impact the airway wall according to particle size (sedimentation). Normally, the particles, including bacteria and similar-sized particles, are trapped in the mucus at this level of more proximal airways and are transported cephalad by the constant motion of the cilia, an apical feature of the respiratory epithelium, at a rate of approximately 2.5 mm/minute in the bronchi but over 5 mm/minute in the trachea. Lower airway mucus is usually cleared in about 24 hours, although this can be drastically retarded in disease states, such as cystic fibrosis or chronic bronchitis, or conditions altering ciliary function or growth, such as tobacco smoking.⁸ The filtering processes appear effective down to particles approximately 0.01 micron in diameter.

Upper Airway Gas Flow

Gas flow is directly proportional to the pressure gradient (change in airway pressure [ΔP]) and inversely proportional to the resistance. When a gas (or liquid) flows through a straight unbranched tube, flow will usually be laminar and resistance is directly proportional to the viscosity of the gas and inversely proportional to the fourth power of the radius.

$$\text{Resistance} = 8 \times \text{length} \times (\text{viscosity} / \pi) \times (\text{radius})^4$$

However, at very high flow rates or when gas flows through an irregular tube or orifice, flow tends to become turbulent and resistance becomes proportional to the density of the gas and inversely proportional to the fifth power of the radius (ie, changes in airway caliber affect resistance to turbulent flow more than laminar flow). Reynolds number is a dimensionless number that allows estimation of whether a flow is turbulent or laminar.⁹

$$\text{Reynolds number} = \text{velocity} \times \text{diameter} \times \text{density} / \text{viscosity}$$

In the airway, Reynolds numbers for air during quiet breathing are <2,000 throughout most of the upper and lower airway (**Figure 24.4**). Reynolds numbers >4,000 are associated with turbulent flow, and 2,000 to 4,000 is a mixture of laminar and turbulent flows. Helium is a gas with a low density compared to air or oxygen; however, the viscosity of the three is almost equal. A mixture of 80% helium/20% oxygen has a density approximately 0.33 that of air and 0.30 that of oxygen. In conditions of increased turbulent flow in large airways due to a mass or edema, breathing a mixture of helium and oxygen will decrease dyspnea for some patients (this is also why breathing helium changes phonation so that a person may imitate Donald Duck). This applies only to turbulent flows in large airways. Helium does not relieve dyspnea due to increased distal laminar airflow resistance such as in asthma or chronic obstructive pulmonary disease (COPD).

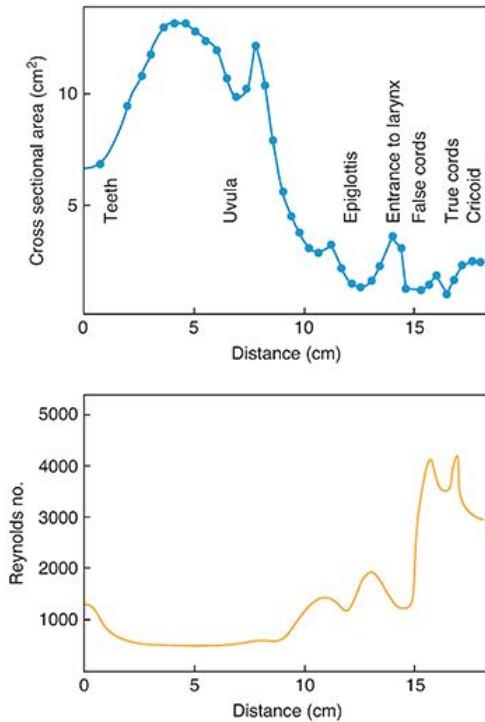


FIGURE 24.4 The cross-sectional area of the upper airway at various levels from the teeth to the cricoid cartilage (top) and the corresponding Reynolds numbers at each level (bottom) for air during a quiet inspiration (flow = 0.5 L/second). Flow will be laminar at Reynolds numbers <2,000 and turbulent at numbers >4,000. *From Burwell DR, Jones JG. The airways and anaesthesia—I. Anatomy, physiology and fluid mechanics. Anaesthesia. 1996;51(9):849-857. Copyright © 1996 The Association of Anaesthetists of Great Britain and Ireland. Reprinted by permission of John Wiley & Sons, Inc.*

Tracheal and Bronchial Structure

The trachea originates at the cricoid cartilage (at the level of C6 vertebra) and extends approximately 10 to 12 cm (females) and 12 to 14 cm (males) to terminate in a bifurcation (carina) at the T4/5 vertebral level (2nd intercostal space, the angle of Louis) (**Figure 24.5**). The trachea is 22 ± 1.5 mm (males) to 19 ± 1.5 mm (females) in diameter and consists of 16 to 20 U-shaped cartilaginous rings that are closed posteriorly by fibrous tissue and a longitudinal smooth muscle band, the trachealis muscle.

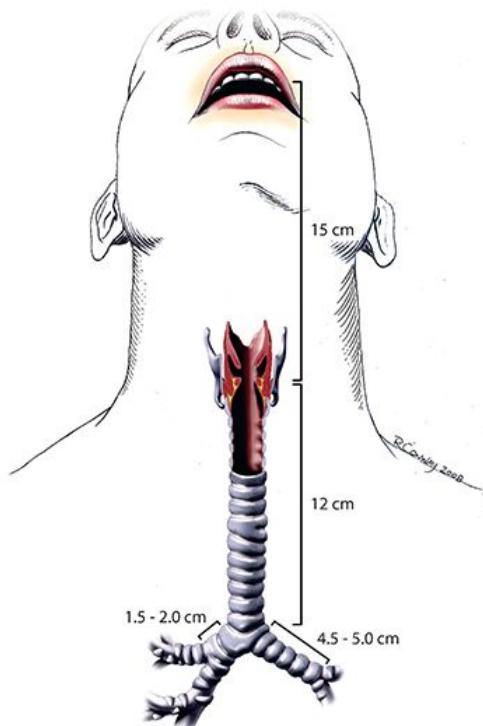


FIGURE 24.5 The average length from the incisors to the vocal cords is approximately 15 cm, and the distance from the vocal cords to the tracheal carina is 12 cm. The average distance from the tracheal carina to the takeoff of the right upper bronchus is 2.0 cm in men and 1.5 cm in women. The distance from the tracheal carina to the takeoff of the left upper and left lower lobe is approximately 5.0 cm in men and 4.5 cm in women. These anatomic distances apply to individuals with a height of 170 cm. Reprinted by permission from Springer: Campos J. Lung isolation in patients with difficult airways. In: Slinger P, ed. Principles and Practice of Anesthesia for Thoracic Surgery. New York, NY: Springer; 2011:247-258. Figure 17.1. Copyright © 2011 Springer Science+Business Media, LLC.

The right main bronchus is wider (16 vs 13 mm), shorter (1.5-2.5 cm vs 4.5-5.0 cm), and more vertical than the left. The right main bronchus gives off the upper lobar bronchus and then continues as the bronchus intermedius giving off the right middle lobar bronchus and right lower lobar bronchus at the hilum of the lung at T5 ([Figure 24.6](#)). The left main bronchus passes inferiorly and laterally below the aortic arch, anterior to the esophagus and descending thoracic aorta, to reach the hilum of the left lung at T6. These dimensions can be quite variable among individuals, and chest pathology can drastically change the anatomy.

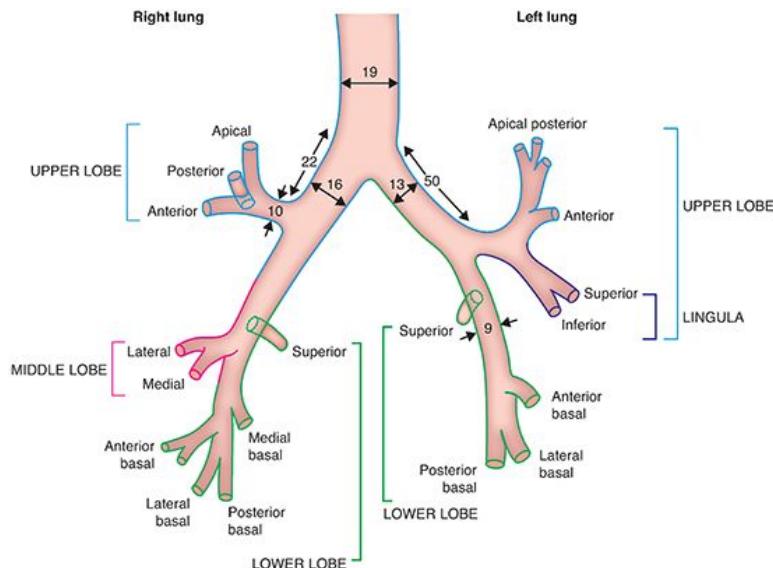


FIGURE 24.6 Diagram of the trachea, lobar, and segmental bronchi showing median lengths and diameters for a 170-cm-tall patient. The lengths and diameters of the bronchi vary considerably between individuals.

The lobar bronchi (right upper, right middle, right lower and the left upper, left lower) extend into their segmental bronchi that can be readily visualized during flexible bronchoscopy. The right upper lobe bronchus gives off 3 segmental bronchi (apical, anterior, posterior) ([Figure 24.7](#)), the right middle lobe bronchus splits into 2 segmental bronchi (lateral, medial), and the right lower lobe bronchus divides into a superior segment (directed posteriorly) and a basilar segmental bronchus, which divides into 4 segments (medial basal, anterior basal, lateral basal, posterior basal) for a total of 10 segmental branches on the right. The left upper lobar bronchus splits into the superior division with “3” segments (a “fused” apical-posterior and an anterior) and the inferior division or lingual with 2 segments (superior and inferior). The left lower lobe bronchus branches into 4 lower segmental branches (superior, a “fused” anteromedial basal, lateral basal, and posterior basal) for a total of “10” segments on the left. An online interactive bronchoscopy simulator is available to demonstrate this anatomy ([Figure 24.8](#)).

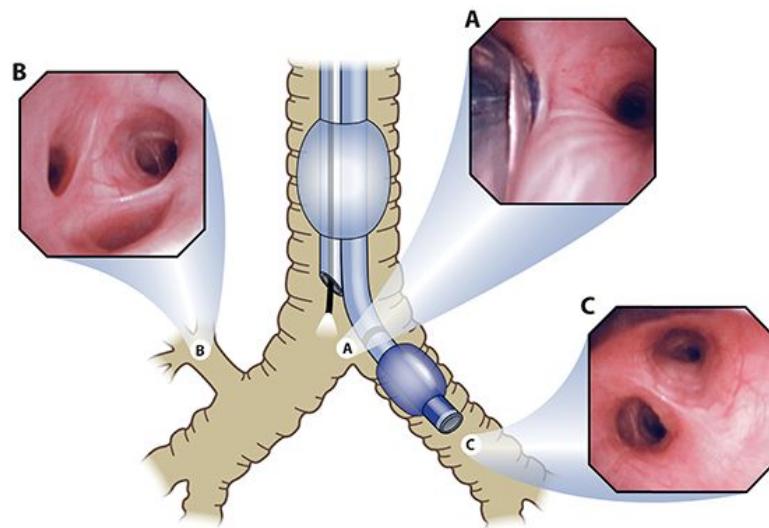


FIGURE 24.7 Bronchial anatomy as seen through a fiberoptic bronchoscope via a properly positioned left-sided double-lumen tube. A, A view of the tracheal carina showing the orifice of the right mainstem bronchus and the bronchial lumen of the double-lumen tube in the left main bronchus. B, The right upper bronchus showing the three segments (this trifurcation is unique in the bronchial tree and a useful landmark). C, A

view of the left mainstem bronchus showing the left upper (top) and lower (bottom) lobe bronchi. *Reprinted by permission from Springer: Campos J. Lung isolation. In: Slinger P, ed. Principles and Practice of Anesthesia for Thoracic Surgery. New York, NY: Springer; 2011:227-246. Figure 16.7. Copyright © 2011 Springer Science+Business Media, LLC.*

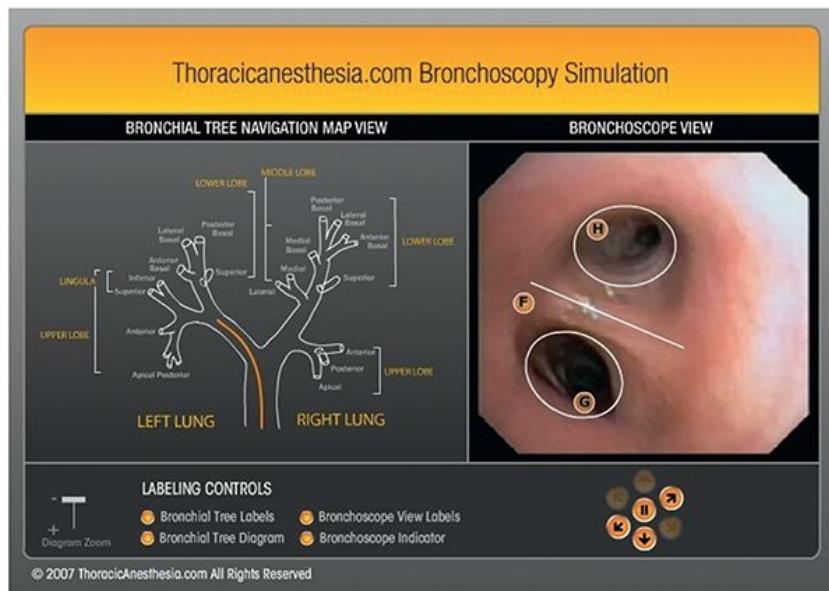


FIGURE 24.8 The free online bronchoscopy simulator at www.thoracicanesthesia.com. The user can navigate the tracheobronchial tree using real-time video by clicking on the lighted directional arrows under the “Bronchoscope View” (right). Clicking on the labels on the “Bronchoscope View” gives details of the anatomy seen. The process is aided by the “Bronchial Tree Navigational Map View” (left), which shows the simultaneous location of the bronchoscope as the orange line in the airway.

Respiratory Airways and Alveoli

The airways continue to divide into smaller diameter conduits until one arrives at the bronchioles with diameters less than 0.8 mm. At this level, the airways lose all remnants of cartilage and begin the transformation from purely conducting airways to those described as respiratory bronchioles. Respiratory bronchioles eventually divide into the final four generations of alveolar ducts, which then consist primarily of openings into the terminal alveolar sacs. In the descriptive model of Weibel ([Figure 24.9A](#)),¹⁰ the trachea branches into 23 generations of airways. The first 15 generations serve as conducting airways and the subsequent 8 generations become sufficiently thin walled to allow some degree of gas exchange and are called **acinar** airways. One clinical aspect of this geometric progression of increasingly narrower airways (and blood vessels) by divergence and multiplication is that the overall cross-sectional area and therefore resistance to gas flow (or blood flow) becomes markedly less compared to the resistance of the proximal airway (or blood vessel) ([Figure 24.9B](#)). This has an important impact on distribution of gas and blood flow, flow velocity, and, hence, transit time through key areas of gas exchange.

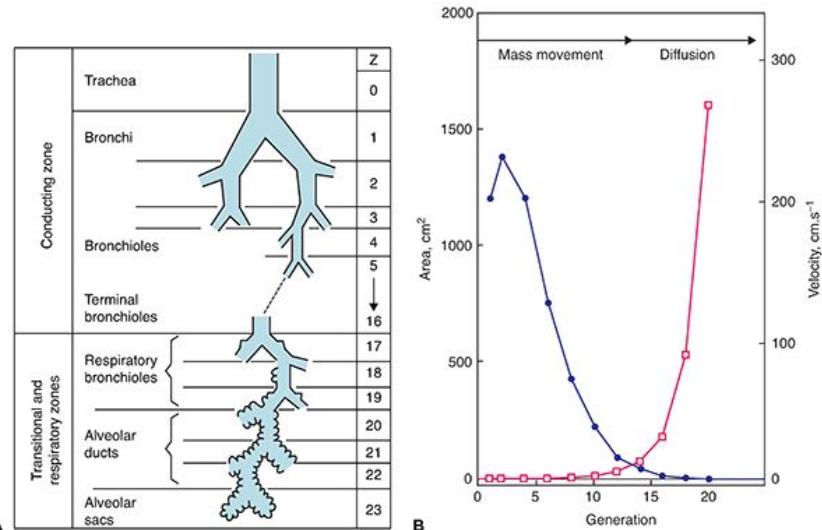


FIGURE 24.9 A, The symmetrical branching model of the tracheobronchial tree. B, The change in cross-sectional area (open squares) and gas velocities (closed circles) seen with normal quiet breathing. Mass movement of gas predominates down to the 14th/15th generation of bronchi below which diffusion becomes the predominant method of gas exchange. The airway dead space is the volume of the airways through which mass movement predominates. *From Burwell DR, Jones JG. The airways and anaesthesia—I. Anatomy, physiology and fluid mechanics. Anaesthesia. 1996;51(9):849-857. Copyright © 1996 The Association of Anaesthetists of Great Britain and Ireland. Reprinted by permission of John Wiley & Sons, Inc.*

The interior of the trachea is lined with ciliated columnar epithelium, goblet cells (responsible for mucus production) (Figure 24.10), and interspersed specialized chemical and tactile neuroreceptors. The lining of the airways transitions from pseudostratified columnar epithelia in the larger bronchi to a thinner cuboidal ciliated variety in the small bronchi. The airway epithelium and submucosa also contain lymphocytes, mast cells, and a variety of neuroendocrine cell types. The next layer consists of circumferential bands of smooth muscle cells and a connective tissue layer containing submucosal glands and plates of cartilage (replacing the solid cartilage rings in the very large airways) (Figure 24.11). The outermost layer is a loose adventitial shell with lymphatic vessels, sympathetic and parasympathetic nerves, and nourishing blood vessels.

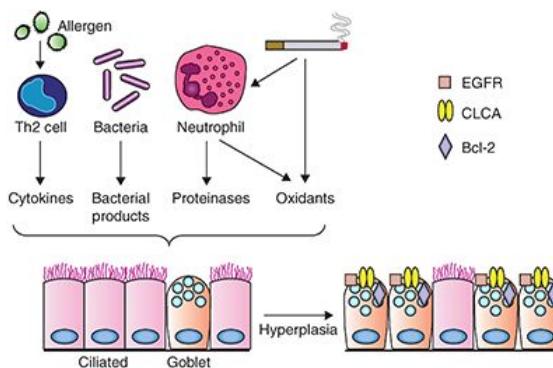


FIGURE 24.10 Normal respiratory epithelium (bottom left) has a predominance of ciliated to goblet cells. Goblet cell hyperplasia (lower right) occurs in response to chronic inflammatory stimuli (upper left), which upregulate mucin production and/or induce goblet cell hyperplasia with associated increases in expression of epidermal growth factor receptors (EGFR), calcium-activated chloride channels (CLCA) and the antiapoptotic factor B-cell lymphoma 2 (Bcl-2). *Modified by permission from Springer: Yeazell L, Littlewood K. Nonrespiratory functions of the lung. In: Slinger P, ed. Principles and Practice of Anesthesia for Thoracic*

Surgery. New York, NY: Springer; 2011:103-119. Figure 7.3. Copyright © 2011 Springer Science+Business Media, LLC.

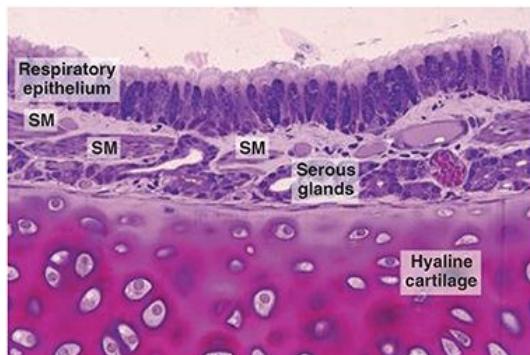


FIGURE 24.11 Microphotograph of a histologic section of the wall of an intrapulmonary bronchus. The mucosa, as in the trachea and extrapulmonary bronchi, consists of an epithelium (ciliated pseudostratified columnar with goblet cells), a basement membrane, and a lamina propria. The latter is rich in elastic fibers of the recoil mechanism. Unlike more proximal air passages, a muscularis is present and lies just external to the lamina propria. It is composed of two sets of smooth muscle (SM) fibers, which extend down the bronchial tree in a right and left spiral. The submucosa is a layer of loose connective tissue, which lies outside the muscularis. Bronchial glands are present in this layer and also extend into the intercartilaginous intervals. The cartilage-fibrous layer lies outside the submucosa. It contains discontinuous plates of hyaline cartilage and fibrous connective tissue. *Repubublished with permission of McGraw Hill LLC from Junqueira LC, Carneiro J. Basic Histology: Text and Atlas. 10th ed. New York, NY: Lange Medical Books/McGraw Hill, 2003; permission conveyed through Copyright Clearance Center, Inc.*

The respiratory bronchioles terminate in a pulmonary acinus, which has the appearance of a cluster of grapes on a network of stems. Each acinus may contain multiple alveolar ducts communicating with 2,000 alveoli arranged in a ringlike, honeycomb network. The alveolus is considered the primary site of gas exchange between the blood and gas in the lung. The alveolar septa are about 5 to 8 microns thick and are opposed by an alveolar surface on either side with the alveolar capillary bed sandwiched inside. The walls of the alveoli are extremely thin, between 0.1 and 0.2 microns, a feature that promotes rapid equilibration of gas by diffusion with the pulmonary capillary blood. In addition, gas can exchange between alveoli through pores of Kohn. There are approximately 300 million alveoli in the human lung, which provides an extraordinary surface area for gas exchange (eg, 70 m²).

There are three major cell types found in the alveolus: alveolar type I cells, alveolar type II cells, and alveolar macrophages. However, there are other cell types found under certain conditions in the lung (eg, inflammation). Alveolar type I cells are squamous epithelial cells that cover most of the alveolar surface. These nucleated cells have few cytoplasmic organelles and a sparse cytoplasm splayed out in sheets over the alveolar surface forming a thin barrier between the air space and the pulmonary capillary endothelium. Alveolar type II cells are fewer in number, somewhat spherical, and coated on their apical surface with microvilli. In contrast to type I cells, alveolar type II cells possess many organelles including multilayered granular structures called **lamellar bodies** ([Figure 24.12](#)). These lamellar bodies are the source of pulmonary surfactant, a lipoprotein coating the interior surface of the alveolus and capable of significantly reducing the surface tension of the alveolus air-surface interface. Surface tension reduction is considered an important physical mechanism to reduce any tendency for alveolar collapse at very low lung volumes.

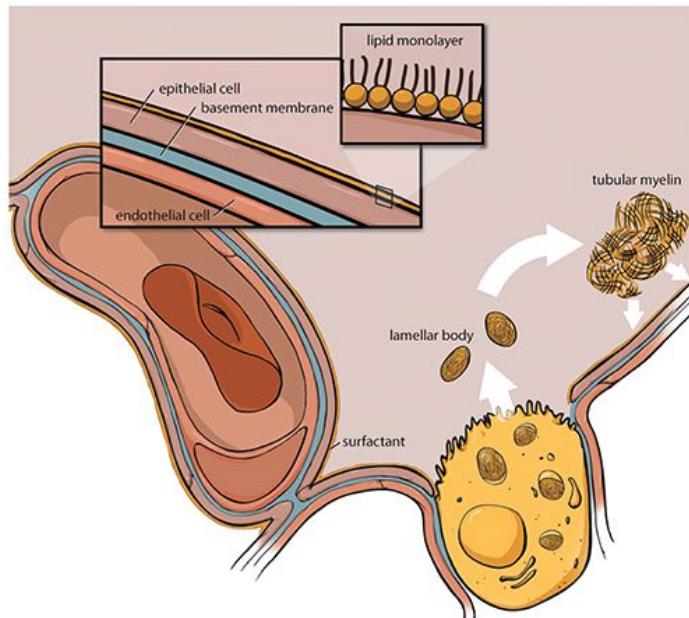


FIGURE 24.12 The diagram presents a scheme of the alveolar air-blood barrier, which consists of endothelial cells, epithelial cells (type I pneumocytes), and their common basement membrane. The large cuboidal cell (bottom right) is a type II pneumocyte producing surfactant, contained within its cytoplasm as lamellar bodies (onion-like structures), which are exocytosed into the alveolar lumen, then transform into tubular myelin and finally form surfactant (lipid monolayer) covering the surface of type I pneumocytes. The upper left-hand side inset shows details of the thin alveolar-capillary membrane; the right-hand side inset shows a scheme of the surfactant monolayer. *Modified by permission from Springer: Wasowicz M. Anesthesia for combined cardiac and thoracic procedures. In: Slinger P, ed. Principles and Practice of Anesthesia for Thoracic Surgery. New York, NY: Springer; 2011:453-464. Figure 32.1A. Copyright © 2011 Springer Science+Business Media, LLC.*

The immune defenses of the lung are extremely important because of the direct exposure of this organ to the external environment via the airways. There are a number of excellent reviews of the immune function of the lung, but it is important to realize that there are many questions unanswered about how the lung responds to invasion and inflammation. From a clinical standpoint, the pulmonary inflammatory response will greatly influence the perioperative management of the surgical patient. A few major defensive cell types residing in the alveolar spaces and interstitium are worth mentioning. Alveolar macrophages are derived from bone marrow monoblast precursor cells and migrate to the lung parenchyma ([Figure 24.13](#)).¹¹ Alveolar macrophages are free to move over the surface of the alveolus and phagocytize foreign material that enters the alveolus including bacteria and particulates. Macrophages are cleared either through the lymphatics or are carried up and expelled via the airways. Lymphocytes, largely T lymphocytes, are widely distributed in the normal lung within paratracheal and hilar lymph nodes, in the interstitium of the bronchial tree as nodules or individual cells and in the alveolar walls. They play a critical role in the lung's primary immune response to inhaled antigens. Under some pathologic conditions in the lung, it is becoming apparent that an exaggerated inflammatory response and the activity of these cells and others may be harmful to the lung; the acute respiratory distress syndrome (ARDS) and emphysema are examples.

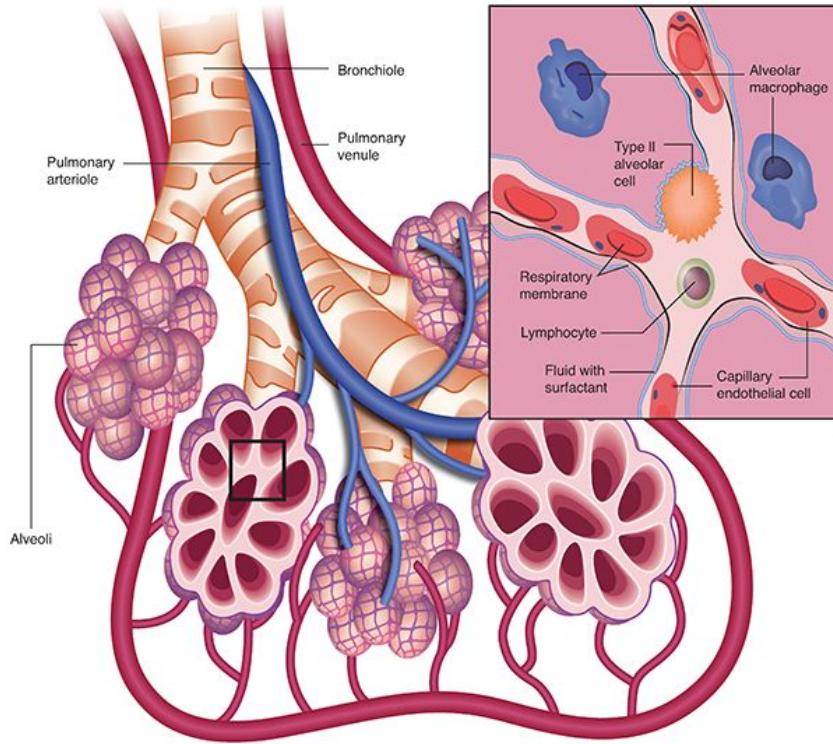


FIGURE 24.13 Diagram of a normal acinus of the lung showing the pulmonary capillaries. In the enlargement (upper right) the macrophages move freely into and out of the alveoli; however, the lymphocytes normally remain within the pulmonary capillaries. Reprinted with permission from Duggan M, Kavanagh BP. Pulmonary atelectasis: a pathogenic perioperative entity. *Anesthesiology*. 2005;102(4):838-854. Copyright © 2005 American Society of Anesthesiologists, Inc.

Pulmonary Circulation

Although the blood flow through the pulmonary circulation is normally equal to the blood flow through the systemic circulation (a major exception being intracardiac shunting when it exceeds systemic circulation), the pressures in the pulmonary circulation are normally lower than the systemic circulation because the pulmonary vascular resistance (PVR) is lower than the systemic resistance (approximately one-sixth of systemic resistance). This is because the pulmonary vessel walls contain less elastic and muscular tissue than systemic vessels of corresponding caliber. Pulmonary arterioles contract rapidly in response to hypoxemia in the alveoli and to a lesser extent to hypoxemia in mixed venous blood. This hypoxic pulmonary vasoconstriction (HPV) is unique to the pulmonary circulation (systemic arterioles dilate in response to hypoxia) and permits regional matching of perfusion to ventilation.

Like all endothelium, the vascular luminal wall of the pulmonary capillaries is lined by glycocalyx, a microcilia layer that acts as a molecular sieve.¹² This >0.1-micron layer prevents adhesion of platelets and leukocytes and is thought to trap larger molecules close to the endothelial membrane and locally increase the oncotic pressure. The glycocalyx covers the pores between endothelial cells and acts as a molecular sieve to control fluid flux. A healthy glycocalyx is important to prevent edema formation in the lung. However, the glycocalyx is damaged by inflammation and ischemia reperfusion, and this may contribute to the increased flux of fluid into the pulmonary extracellular matrix in these conditions.

The air passages receive their blood supply from systemic bronchial arteries down to the level of the respiratory bronchioles. Only one-third of the bronchial circulation returns to the systemic venous system, the remainder drains into the pulmonary veins, and this constitutes the largest portion of the normal extrapulmonary venoarterial shunt. This bronchial shunt is less than 1% of the cardiac output in healthy individuals but may increase to 10% in bronchiectasis, emphysema, and some congenital cardiac conditions.

Thorax and Muscles of Respiration

The lungs are contained within the thorax. The bony thorax is composed of the 12 ribs, the sternum anteriorly, and the thoracic vertebral column posteriorly. The caudal end of the thorax is formed by the diaphragm, and the cranial end of the thorax is the thoracic inlet, within the ring formed by the first ribs, containing the trachea, esophagus, and the neurovascular supply to the head and arms. Bulk movement of air into and out of the lungs occurs as a result of changes in intrathoracic pressure created by rhythmic changes in the volume of the thorax. Expansion of the chest cavity occurs when three respiratory muscle groups work in concert. The diaphragm, intercostal muscles, and the accessory muscles (sternocleidomastoids, scalenes) are controlled by the respiratory centers of the brain to contract in a rhythmic pattern designed to match ventilation to gas exchange requirements. The abdominal musculature (rectus abdominis, external oblique, internal oblique, and transversus abdominis) can be recruited when more force is required for exhalation, although abdominal muscle tone may stabilize the rib cage during inspiration as well.¹

Inspiration

The diaphragm is unique in that its muscle fibers radiate from a central tendinous structure to insert peripherally on the ventrolateral aspect of the first three lumbar vertebrae, the aponeurotic arcuate ligaments, the xiphoid process, and the upper margins of the lower six ribs. Its motor innervation is solely from the right and left phrenic nerves, which originate from the 3rd, 4th, and 5th cervical spinal nerves. In the relaxed state, it forms a pronounced “dome” that closely apposes the chest wall for some distance before arching across. Contraction of the diaphragm causes a large caudal displacement of the central tendon resulting in a longitudinal expansion of the chest cavity. Simultaneously, its insertions on the costal margins cause the lower ribs to rise and the chest to widen. This diaphragmatic motion is responsible for the majority of quiet respiration. As the dome descends, it displaces the abdominal contents caudally. The fall in pleural pressure and accompanying lung expansion produce an increase in abdominal pressure and outward movement of the abdominal wall. The supine and Trendelenburg positions or surgical retractors can significantly interfere with this abdominal motion especially in the morbidly obese, necessitating controlled ventilation under anesthesia.

The intercostal muscles are thin, sheetlike muscles with origins and insertions between the ribs. The internal intercostal muscles have their fibers oriented obliquely, caudally, and dorsally, from the rib above to the rib below. The external intercostal muscles have their fibers oriented obliquely, caudally, and ventrally, from the rib above to the rib below. All intercostals are innervated by the intercostal nerves running in the neurovascular bundle under the inferior lip of each rib. The contraction of the external intercostal muscles produces an inspiratory action by elevating the upper ribs to increase the anteroposterior dimensions of the chest in a “bucket-handle” motion. The lower ribs are also elevated by virtue of the force applied and their point of rotation to increase the transverse diameter of the thorax. The internal intercostals apply their force in such a direction as to rotate the ribs downward, decreasing the thoracic anteroposterior dimension to aid in active expiration (when required) and cough. In general, the intercostal muscles do not play a major role in quiet respiration but do in exercise or other conditions requiring high levels of ventilation.

The principal accessory respiratory muscles are the sternocleidomastoid and scalene muscles. The scalene muscles originate from the transverse processes of the 4th through the 8th cervical vertebrae and slope caudally to insert on the first two ribs. Their contraction during periods of high ventilatory demand elevates and fixes the cephalad rib cage during inspiration. Similarly, the sternocleidomastoid muscles elevate the sternum and increase the longitudinal dimensions of the thorax.

Expiration

Expiration is a passive process in quiet breathing and is largely the response to relaxation of the inspiratory muscles and the balance of forces generated by the elastic recoil of the lungs and chest wall. When high levels of ventilation are required as in exercise or if airway resistance increases (as in exacerbations of asthma or COPD), the expiratory phase becomes an active process with forceful contraction of the rectus abdominis, the transverse abdominis, and the internal and external oblique muscles. The contraction of the abdominal musculature retracts the abdominal wall and pulls the lower ribs downward, which increases intraabdominal pressure and accelerates the cephalad displacement of the diaphragm during exhalation. The internal

intercostal muscles depress the rib cage and provide a minor contribution to forced expiration. Innervation of the abdominal musculature is from thoracic nerves 7 through 12 and the 1st lumbar nerve.

Like most skeletal muscles, the diaphragm and intercostal muscles contain a heterogeneous mix of fiber types. The diaphragm has between 49% and 55% type I (slow-oxidative) fibers, the remainder a mix of the “faster high activity” types IIA and IIB fibers.¹³ The types of skeletal muscle fibers are distributed fairly evenly throughout the diaphragm. Of note, the respiratory muscles retain the ability to adapt to stress and training. This includes responses to lung pathology, which might seem maladaptive. Emphysema is a good example. The diaphragm undergoes changes at the sarcomere level, physically “losing” contractile units as hyperinflation of the lungs leads to increasing thoracic dimensions and “flattening” of the diaphragm.¹⁴ Loss of sarcomeres in series with the central tendon may help to restore the mechanical advantage of the optimal length-tension relationship for the muscle.

Respiratory Mechanical Function

The basics of mechanical function of the respiratory system are the interaction of two opposing springs: the chest wall, which at rest is trying to expand, and the lungs, which at rest are trying to contract ([Figure 24.14](#)). The lungs and chest wall move together as a unit. This is made possible by the enclosed, airtight thoracic cavity where the outer surface of the lungs and its visceral pleura are in close proximity to the parietal pleura covering the inner surface of the chest wall and the mediastinal structures. Changes in the intrathoracic volume are only possible because the inside of the lung is in continuity with the ambient atmosphere outside the thorax via the trachea and pharynx. The intimate contact between the layers of pleura is maintained by a negative intrapleural pressure generated in part by the intermolecular forces of the pleural fluid excluding gas from this space. This lubricating fluid allows freedom of the pleural layers to slide over one another but highly resists separation of the layers much like two panes of glass with a thin layer of water between them.

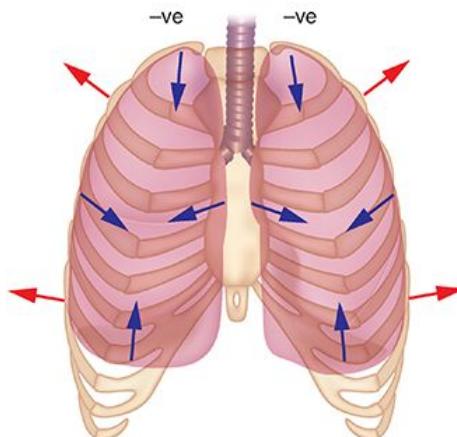


FIGURE 24.14 The respiratory system is at an elastic equilibrium at rest at functional residual capacity. The outward recoil of the chest wall (red arrows) is balanced by the inward recoil of the lungs (blue arrows). The opposing forces generate the negative intrathoracic pressure (mean approximately $-5\text{ cm H}_2\text{O}$) with a superior-inferior gradient due to gravitational effects on the lung parenchyma.

Normally, the intrapleural pressure is about $-5\text{ cm H}_2\text{O}$ when the respiratory system is at equilibrium. Because of the deforming effect of gravity on the lung parenchyma, there is a vertical gradient of intrapleural pressure. This gradient is largest in the seated or upright position ([Figure 24.15](#)). The volume of gas contained in the lungs at this resting point is termed **functional residual capacity**. For a healthy young adult male, total lung capacity (TLC) will be approximately 6 to 6.5 L and FRC will be 2.5 to 3 L. The oxygen contained in the FRC (500-600 mL) is the only reservoir of oxygen in the body.

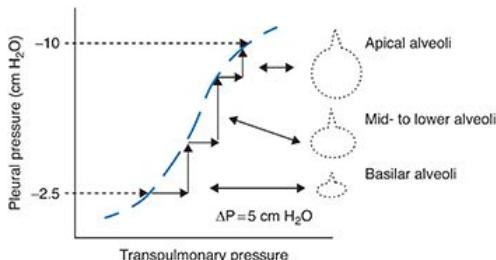


FIGURE 24.15 The static relationship between the transpulmonary pressure (alveolar pressure – pleural pressure) and the pressure in the pleural space results in a sigmoid curve of respiratory compliance. Pleural pressure is normally negative relative to atmospheric pressure. In the seated or upright position, the gradient is small at the base of the lung (intrapleural pressure [P_{PL}] least negative) but larger at the apex (P_{PL} most negative) because of the deforming effect of gravity on the lung parenchyma. This disparity results in larger alveoli at the apex and then the dependent alveoli at the base. As a result of this sigmoid relationship, a given change in transpulmonary pressure produces the largest change in volume (and pleural pressure) where the alveoli are on the steepest portion of this curve (mid to lower alveoli). *Reprinted by permission from Springer: Jaeger JM, Blank RS. Essential anatomy and physiology of the respiratory system and the pulmonary circulation. In: Slinger P, ed. Principles and Practice of Anesthesia for Thoracic Surgery. New York, NY: Springer; 2011:51-69. Figure 4.3. Copyright © 2011 Springer Science+Business Media, LLC.*

Pathologic conditions such as the introduction of air or blood into the intrapleural space can rapidly disrupt this lung–chest wall interaction, leading to a compromise in respiratory function but also interfere with cardiovascular function. Examples of disruption of the intrapleural space would be a pneumothorax, empyema, pleural effusion, or bronchopleural fistula.

Lung Volumes and Spirometry

By convention, the static and dynamic subdivisions of gas contained within the lung are given a common nomenclature of volumes and capacities (Table 24.1 and Figure 24.16). Volumes are most commonly measured by spirometry (Figures 24.17 and 24.18) and capacities are then calculated as the sum of specific volumes. Simple spirometry can give all of the volumes and capacities listed in Table 24.1 except FRC, TLC, and residual volume (RV), all of which require a separate measurement of RV. The RV can be measured by washin or washout dilution calculations using a relatively insoluble gas such as nitrogen or helium and a closed breathing circuit. In modern pulmonary function labs, these laborious techniques have largely been replaced by whole-body plethysmography, which is both simpler and more accurate (Figure 24.19), which measures FRC, and this can be used to calculate RV by subtraction of expiratory reserve volume measured by spirometry.

TABLE 24.1

Lung volumes and capacities

Lung volumes	Definition
Tidal volume (VT)	Air volume inspired and expired during a relaxed breathing cycle
Residual volume (RV)	Volume remaining in the lung after a maximal expiratory effort
Expiratory reserve volume (ERV)	The volume of air that can be forcibly exhaled between the resting end-expiratory volume and RV
Inspiratory reserve volume (IRV)	The volume of air that can be inspired with maximal effort above the normal resting end-expiratory position of a VT
Forced expiratory volume in 1 second (FEV ₁)	The volume of air that can be exhaled in 1 second with maximal effort from the point of maximal inspiration
Lung capacities	
Vital capacity (VC)	The amount of air that can be exhaled from the point of maximal inspiration to

	the point of maximal expiration (IRV + ERV)
Forced vital capacity (FVC)	The volume of air that can exhaled with maximal effort from TLC
Total lung capacity (TLC)	Total volume of air in the lungs after a maximal inspiration (IRV + ERV + RV)
Functional residual capacity (FRC)	Amount of air in the lung at the end of a quiet exhalation (ERV + RV)

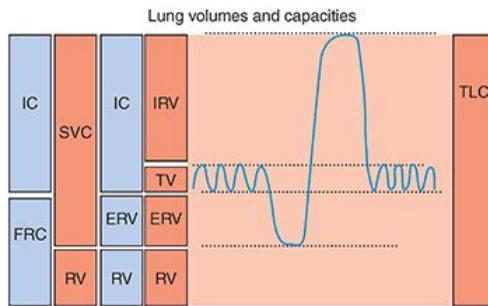


FIGURE 24.16 Complete pulmonary function testing will provide data on lung volumes and capacities to differentiate obstructive from restrictive lung diseases. Functional residual capacity (FRC) = expiratory reserve volume (ERV) + residual volume (RV). Measuring closing volume and closing capacity requires insoluble gas washout techniques and is not included in routine pulmonary function testing. However, an appreciation of the variable relationship between closing capacity and FRC and the effects of anesthesia on FRC is essential for the anesthesiologist to understand the changes in gas exchange that occur during anesthesia. Abbreviations: IC, inspiratory capacity; IRV, inspiratory reserve volume; SVC, slow vital capacity; TLC, total lung capacity; TV, tidal volume. *Reprinted by permission from Springer: Slinger P, Darling G. Preanesthetic assessment for thoracic surgery. In: Slinger P, ed. Principles and Practice of Anesthesia for Thoracic Surgery. New York, NY: Springer; 2011:11-34. Figure 2.5. Copyright © 2011 Springer Science+Business Media, LLC.*

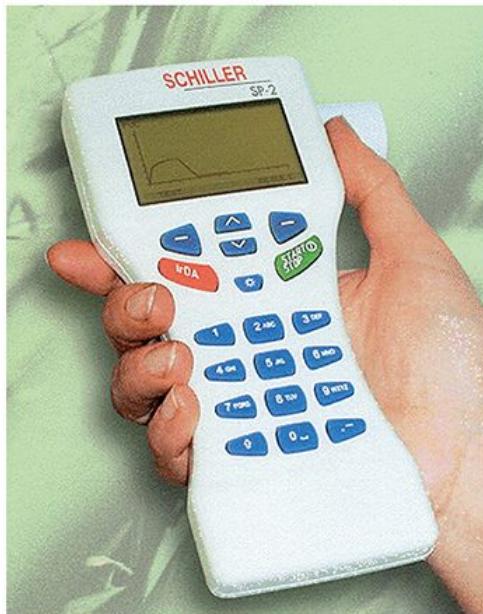


FIGURE 24.17 An example of a portable handheld spirometer that can be easily used in the preoperative assessment clinic or at the bedside to measure the majority of the clinically important lung volumes and capacities. *Reprinted by permission from Springer: Slinger P, Darling G. Preanesthetic assessment for*

thoracic surgery. In: Slinger P, ed. Principles and Practice of Anesthesia for Thoracic Surgery. New York, NY: Springer; 2011:11-34. Figure 2.3. Copyright © 2011 Springer Science+Business Media, LLC.

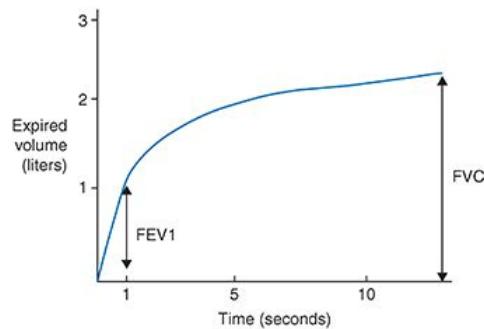


FIGURE 24.18 A simple spirogram. Expired volume is plotted against time. The total volume exhaled during a forced expiration from total lung capacity is the forced vital capacity (FVC). The fraction of the FVC that is exhaled in the first second is the forced expiratory volume in 1 second (FEV_1). These values are compared to normal data for age, sex, and height and given a percentage of predicted value (eg, $FEV_1\%$).

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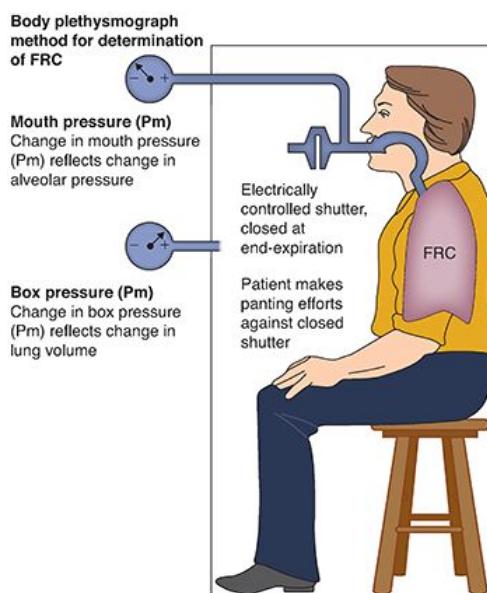


FIGURE 24.19 Complete measurement of lung volumes and capacities is commonly performed in the pulmonary function lab by whole-body plethysmography with the patient seated in an airtight box. Lung volumes can be calculated from changes in the airway and box pressure because the volume of the box is known. Abbreviation: FRC, functional residual capacity. Reprinted by permission from Springer: Slinger P, Darling G. Preanesthetic assessment for thoracic surgery. In: Slinger P, ed. Principles and Practice of Anesthesia for Thoracic Surgery. New York, NY: Springer; 2011:11-34. Figure 2.6. Copyright © 2011 Springer Science+Business Media, LLC.

Spirometry measurements are commonly reported as “observed” (or measured) and “predicted” (Figure 24.20). Predictions are based on population statistical means, which take into account age, sex, and height. For example, an observed forced expiratory volume in 1 second (FEV_1) of 1.0 L for an 85-year-old male, 152

cm in height (5 ft tall) is 85% predicted (within the normal range of $100\% \pm 20\%$) but an FEV₁ of 1.0 L for a 30-year-old male, 182 cm (6 ft) is 20% predicted, which would be consistent with severe end-stage lung disease. The FEV₁, forced vital capacity (FVC), and their ratio (FEV₁/FVC) are the most useful spirometry measurements for the anesthesiologist to assess the severity of a patient's lung disease or to evaluate a patient's operability for lung resection surgery.¹⁵

Test performed	Pred. val.	Pre BD		Post BD	
		Obs.	%Pred. val	Obs.	%Pred. val
Total lung capacity (TLC), L	4.2	7.4	175	---	---
Functional residual capacity (FRC), L	2.6	6.2	239	---	---
Inspiratory capacity (IC), L	1.6	1.2	74	---	---
Vital capacity (VC), L	2.4	1.5	63	---	---
Residual volume (RV), L	1.8	5.9	322	---	---
RV/TLC ratio (RV/TLC), %	43	80	184	---	---
Forced vital capacity (FVC), L	2.4	1.5	62	---	---
Forced exp. volume in 1 sec. (FEV ₁), L	1.7	0.6	34	---	---
FEV ₁ /FVC ratio (FEV ₁ /FVC), %	71	39	55	---	---
Max. Exp. flow @ 50% VC (V50), L/sec	2.4	0.17	7	---	---
Max. Exp. flow @ 25% VC (V25), L/sec	1.2	0.07	6	---	---
Mid expiratory flow 25-75% (FEF 25-75), L/sec	2.0	0.2	12	---	---
Airway resistance (Raw), cmH ₂ O/L/sec	0.7	2.5	387	---	---
Max. voluntary ventilation (MVV), L/min	50	---	---	---	---
Lung diffusion capacity (DLco), ml/min/mmHg	12.6	7.5	59	Normal limits: 75-125%	
VA@BTPS from DLco (VA@BTPS), L	4.2	2.5	60	---	---

Note: %Pred. values are **BOLD** when outside of normal limits. (All except raw & DLco values.)

FIGURE 24.20 A copy of the pulmonary function laboratory test report for a patient with severe emphysema. Of the 15 different results in this report, the 2 results highlighted, the percentage predicted FEV₁ and diffusion capacity for carbon monoxide (DLco), are the most useful tests for the anesthesiologist assessing a patient for possible pulmonary resection. This patient had taken a bronchodilator immediately before the test, so the usual postbronchodilator (post BD) test was not repeated. Abbreviations: BTPS, body temperature and pressure saturated; Obs., patient's measured result; Pred. val., predicted value corrected for the patient's age, sex, and height; VA, the single-breath dilutional estimate of TLC from the DLCO. *Reprinted by permission from Springer: Slinger P, Darling G. Preanesthetic assessment for thoracic surgery. In: Slinger P, ed. Principles and Practice of Anesthesia for Thoracic Surgery. New York, NY: Springer; 2011:11-34.* Figure 2.8. Copyright © 2011 Springer Science+Business Media, LLC.

In addition, complete pulmonary function testing in the laboratory will commonly report measurements of volume ratios, flows, lung resistance, lung diffusion capacity for carbon monoxide, and other measurements. The majority of these other values, although useful for distinguishing among different types and severities of pulmonary diseases in clinical chest medicine, are not commonly used in anesthesia. The exception is the lung diffusion capacity for carbon monoxide, which is a measurement of lung parenchymal function (ie, alveolocapillary gas transfer).

Closing Capacity and Closing Volume

The key to understanding the complex changes that develop in the respiratory system during anesthesia is to appreciate the relationship between FRC and closing capacity (CC). The CC is the sum of closing volume (CV) and RV. The CV is the lung volume below which small airways begin to close (or at least cease to contribute expiratory gas) during expiration. Closure of small airways in the basal portions of the lung during deep expiration is a normal phenomenon due to the gravity-dependent increase in pleural pressure at the bases and due to the lack of parenchymal support in distal airways. The CV and CC are not commonly measured in the pulmonary function lab. Measurement is either by a washin technique with a small bolus of an insoluble tracer gas such as xenon 133 slowly inhaled then exhaled from RV (**Figure 24.21**) or by nitrogen washout after inspiration of a breath of oxygen from RV. Normal values for CC in seated healthy young adults are 15% to 20% of vital capacity.⁵ The CC increases with age due to loss of structural parenchymal

support tissue in the lung and an increase in RV. The FRC increases slightly with age but the increase is greater for CC ([Figure 24.22](#)).¹⁶ The CC changes very slowly over time. However, FRC changes on a minute-to-minute basis as the mechanical advantage of the two springs (lung and chest wall) that determine it changes. The CC exceeds FRC in the supine position at age 45 and in the upright position by age 65. During anesthesia, a decrease in the elastic recoil of the chest wall due to the muscle-relaxing effects of almost all general anesthetics (with the possible exception of ketamine) and neuromuscular blockers causes FRC to decrease, and it will often fall below CC.¹⁷ Similarly, an increase in elastic recoil of the lung due to fluid retention in the pulmonary parenchyma will lower the FRC. When an alveolar unit falls below its CC, even for a brief period during one respiratory cycle, the concentration of oxygen (alveolar PO_2 [PAO_2]) in that unit falls slightly. This results in the increase of venoarterial admixture (“shunt”; see the following text) and decrease in arterial oxygen tension (PaO_2) seen in the elderly and during general anesthesia. When a region of the lung is kept below its CC, the loss in volume will eventually lead to atelectasis ([Figure 24.23](#)) as the gas trapped in the alveoli is absorbed. A large part of the anesthesiologist’s job in the perioperative period is restoring the balance between FRC and CC. Because CC cannot be changed, this involves improving FRC by a variety of techniques to improve the mechanical advantage of the chest wall. These techniques may include ensuring adequate reversal of neuromuscular blockers, upright positioning, regional analgesia, and possibly the use of positive end-expiratory pressure (PEEP) or continuous positive airway pressure (CPAP). The physiologic differences between PEEP and CPAP are subtle. However, by common usage, when positive pressure is applied during expiration to the airway of a patient who is having positive pressure ventilation, this applied airway pressure is referred to as **PEEP**. When a patient is breathing spontaneously, an applied airway pressure is referred to as **CPAP**.

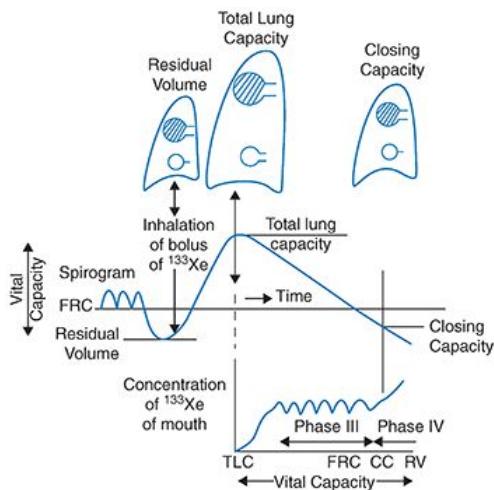


FIGURE 24.21 Measurement of closing capacity (CC) by the use of a tracer gas such as xenon 133 (^{133}Xe). The bolus of tracer gas is inhaled from residual volume and due to closure of some small airways is distributed only to those alveoli whose airways are still open (shown as the shaded areas in the diagram). During expiration, the concentration of the tracer gas becomes constant after the dead space is washed out. This plateau (phase III) gives way to a rising concentration of tracer gas (phase IV) when there is closure of the airways leading to the alveoli, which did not receive the tracer gas. The measured volume from the onset of phase IV until the end of expiration (residual volume [RV]) is the closing volume (CV). The CC is calculated as the sum of CV and RV (which is measured separately, see “[Lung Volumes and Spirometry](#)” section in earlier discussion). *Reprinted from Lumb AB. Nunn’s Applied Respiratory Physiology. 7th ed. Edinburgh: Churchill Livingstone/Elsevier; 2010. Copyright © 2010 Elsevier. With permission.*

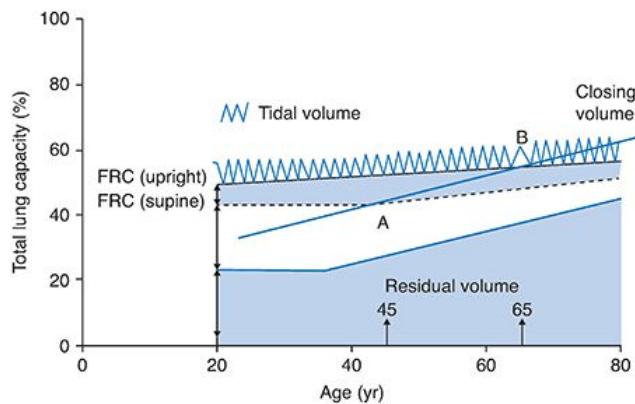


FIGURE 24.22 The effects of aging and position on closing volume, residual volume, and functional residual capacity (FRC) as a percentage of total lung capacity. With aging, there is a slight increase in FRC, but both closing volume and residual volume increase at a greater rate. *Reprinted by permission from Springer: Sprung J, Gajic O, Warner DO. Review article: Age related alterations in respiratory function - anesthetic considerations. Can J Anaesth. 2006;53(12):1244-1257. Copyright © 2006 Springer Nature. Modified with permission from Zaugg M, Lucchinetti E. Respiratory function in the elderly. Anesthesiol Clin North Am. 2000; 18(1):47-58. Copyright © 2000 Elsevier.*

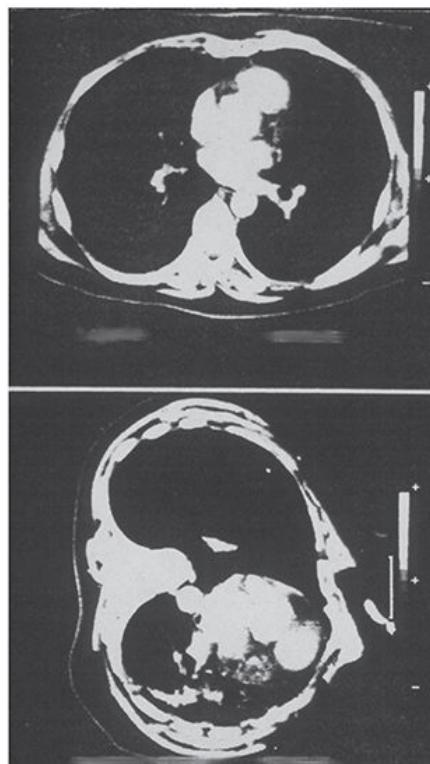


FIGURE 24.23 Thoracic computed tomography scans of a patient awake (top) and then anesthetized and turned to the lateral position (bottom). The dependent lung tends to fall below its closing capacity due to the effect of gravity and the compression of the mediastinum. This results in atelectasis, which can be seen developing in the dependent lung. *Reprinted from Slinger PD, Campos JH. Anesthesia for thoracic surgery. In: Miller RD, ed. Miller's Anesthesia. 7th ed. Philadelphia, PA: Churchill Livingstone/Elsevier; 2010. Copyright © 2010 Elsevier. With permission.*

Compliance

Compliance is the change in lung volume (ΔV) for a given ΔP . It is the reciprocal of “elastance.” Monitoring changes in respiratory compliance is extremely important in ventilated patients as an early warning of changes in the lung or chest–abdominal wall complex that may negatively affect gas exchange. Compliance of the respiratory system (C_{RS}) is measured as the ΔV divided by the ΔP ; this represents the difference between alveolar pressure, at a given lung volume, and ambient (atmospheric) pressure.

$$C_{RS} = \Delta V / \Delta P$$

The C_{RS} is dependent on the interaction of the compliance of the lung itself (C_L) and the compliance of the chest wall (C_{cw}). These two springs act similar to series capacitors in an electrical system, that is, storing energy, and the reciprocal of respiratory compliance is the sum of the reciprocals of C_L and C_{cw} :

$$1/C_{RS} = 1/C_L + 1/C_{cw}$$

C_L is calculated as $\Delta V / \Delta P$, where ΔP = alveolar pressure – intrapleural (“transmural”) pressure.

C_{cw} is calculated as $\Delta V / \Delta P$, where ΔP = intrapleural pressure – ambient pressure.

Intrapleural pressure is not easy to measure directly in the clinical setting. Esophageal pressure, from a balloon manometer, is commonly used as an approximation of intrapleural pressure in respiratory research. As the respiratory system inflates, both the lung and chest will produce their own unique compliance curves ([Figure 24.24](#)).

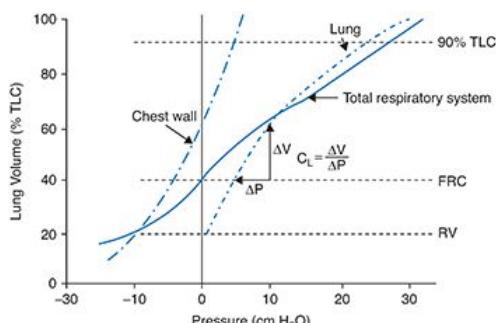


FIGURE 24.24 Static pressure-volume curves of the respiratory system. The isolated chest wall compliance curve (C_{cw}) (large dash-dot line) crosses the zero pressure or equilibrium point at approximately 60% of total lung capacity (TLC). The isolated lung compliance (C_L) (small dash-dot line) approaches its equilibrium point at about 20% TLC or residual volume (RV). The algebraic summation of the reciprocals of C_{cw} and C_L produces the compliance of the total respiratory system (C_{RS}) (solid line). The outward recoil of the chest wall and the inward recoil of the lung will balance at functional residual capacity (FRC). Note that the chest wall will passively contribute to lung inflation up to 60% TLC above which the chest wall will oppose inflation and the compliance (slope of the solid line) will begin to decrease. Abbreviations: ΔP , change in airway pressure; ΔV , change in lung volume. *Reprinted by permission from Springer: Jaeger JM, Blank RS. Essential anatomy and physiology of the respiratory system and the pulmonary circulation. In: Slinger P, ed. Principles and Practice of Anesthesia for Thoracic Surgery. New York, NY: Springer; 2011:51-69. Figure 4.4. Copyright © 2011 Springer Science+Business Media, LLC.*

Factors affecting C_L include the following:

1. Lung volume. Compliance is greatest at FRC and remains at this level until the lung inflates or deflates to approximately 15% of TLC above or below FRC, that is, the slope of C_{RS} is the steepest in

this range, which includes the range of normal tidal volume breathing. Compliance is related to the normal FRC for a given lung and can be corrected for normal lung volume as the “specific compliance” (compliance/FRC), which is relatively constant at all ages.

2. Surface tension of the alveoli. This is probably the major factor determining lung recoil and C_L . A lung that is filled with water is actually more compliant than a normal lung because the air-fluid surface tension interaction is lost. Similarly, a lung that is depleted of surfactant is less compliant than normal. Without surfactant, the alveoli would be expected to behave like communicating bubbles and conform to the Laplace equation:

$$P = 2T / R$$

Where P is the gas pressure within a bubble, T is the surface tension of the wall, and R is the radius of the bubble. If the radius is decreased without a change in surface tension, the pressure will increase in the bubble and a small bubble will empty into a larger bubble (in the lung, this would lead to atelectasis). However, in the lung, surface tension decreases as the radius of the alveoli decreases and this opposes the collapse of smaller lung units. The exact mechanisms by which surfactant causes this effect are debated.¹⁸ It could be related to a tighter packing of surfactant molecules as the radius decreases or the formation of surfactant multilayers. Other factors that affect the C_L include pulmonary blood volume and interstitial edema.

Factors affecting C_{cw} include posture, obesity, ossification of the costal cartilages, and scarring of the skin. The interaction of the compliances of these two springs produces the characteristic sigmoid pattern of the compliance curve of the respiratory system (see [Figure 24.24](#), solid line). At FRC, which is normally the relaxation volume of the respiratory system, the pull of the two springs in opposite directions balance one another. In a normal healthy individual, as the respiratory system inflates to 60% of TLC, the chest wall is aiding the muscles of respiration to inflate the lungs. However, as the lung inflates above this volume, the muscles of inspiration must work to distend both the lungs and the chest wall.

Dynamic compliance is the $\Delta V/\Delta P$ of the respiratory system measured at the instant gas flow. In a ventilated patient, this ΔP will = peak airway pressure – PEEP. This reflects the normal behavior of the respiratory system but will include the effects of airway resistance and the normal hysteresis of the lung parenchyma (hysteresis in this context refers to the tendency of an elastic material to resist change of shape both during stretch and contraction). Dynamic compliance will be affected by both the frequency of respiration and the velocity of gas flow.

Static compliance is the $\Delta V/\Delta P$ of the respiratory system measured at a point of no gas flow and when the pressure gradient has been allowed to equilibrate in the entire airway. This is difficult, but not impossible, to achieve in an awake subject by relaxing at end inspiration against a closed airway. However, it is simple to measure in an anesthetized and paralyzed patient during ventilation in a volume-controlled mode (with a fixed inspiratory flow) by using an end-inspiratory pause. The ΔP for static compliance will = plateau airway pressure – PEEP.

Both static and dynamic compliances provide useful information for the anesthesiologist. The static compliance reflects more the actual distending pressure in the patient’s alveoli. The difference between the two reflects the effects of airway resistance. During pressure-control ventilation, with a decreasing inspiratory airflow pattern, there will not be a discernible difference in the peak or plateau in the airway pressure, so distinguishing between static and dynamic compliance is clinically difficult ([Figure 24.25](#)). This negative, that is, loss of monitoring, aspect of pressure-control ventilation is largely compensated by the ability of pressure-control ventilation to more uniformly distribute gas flow in patients with COPD who have large differences in regional compliance within the lung (see the following text).

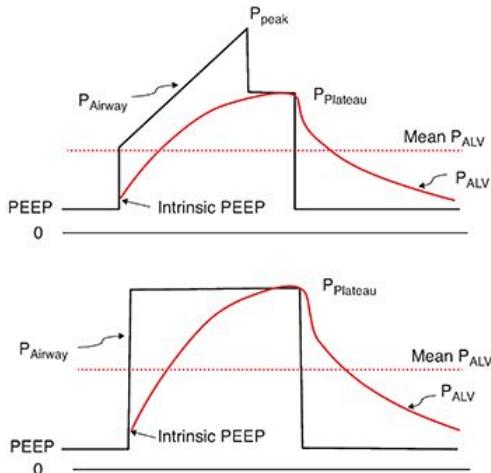


FIGURE 24.25 Comparison of the airway (P_{Airway} , black line) and alveolar (P_{ALV} , red line) pressures (vertical axis) for volume-control ventilation with an end-inspiratory hold (plateau) (top) and pressure-control ventilation (bottom) plotted against time (horizontal axis). For volume-control ventilation, the difference between the peak airway pressure (P_{peak}) and the plateau pressure (P_{Plateau}) represents the resistance to gas flow. This is primarily due to the combined nonelastic resistance of the airway and circuit. This gas-flow resistance cannot easily be monitored during pressure-control ventilation, which has only a P_{Plateau} . Note that the mean P_{ALV} in healthy individuals is approximately the same with the two methods of ventilation for the same tidal volumes. Abbreviation: PEEP, positive end-expiratory pressure. Reprinted by permission from Springer: Ward DS. *Intraoperative ventilation strategies for thoracic surgery*. In: Slinger P, ed. *Principles and Practice of Anesthesia for Thoracic Surgery*. New York, NY: Springer; 2011:297-308. Figure 21.4. Copyright © 2011 Springer Science+Business Media, LLC.

The inflation and deflation limbs of the compliance curve of the respiratory system are different (Figure 24.26). For dynamic compliance, this is due to both airway resistance and lung hysteresis. These curves combine to produce the familiar “pressure-volume loop” (or “PV” or “ $\Delta V/\Delta P$ ” or “compliance” curve) of the lung displayed by many modern anesthetic machines, and its shape is determined mainly by the dynamic C_{RS} . The gap between the expiratory and inspiratory limbs of the combined curve will widen as tidal volume and respiratory rate increase. It is possible to generate a $\Delta V/\Delta P$ curve using static compliance if the lung is slowly inflated in a stepwise fashion. This curve will also show a gap between inspiration and expiration due mainly to lung hysteresis. This gap will be smaller than that for the dynamic $\Delta V/\Delta P$ curve.¹⁹ An automated breath-by-breath calculation of compliance is displayed by the ventilation monitors of many modern anesthetic machines. It is difficult for these clinical monitors to measure at a true static “no flow” point at end inspiration and therefore measured compliance changes may be truly due to increased tissue elastance (eg, atelectasis or pulmonary edema) but may also be affected by changes in dynamic compliance (airway resistance); for example, bronchospasm or secretions.

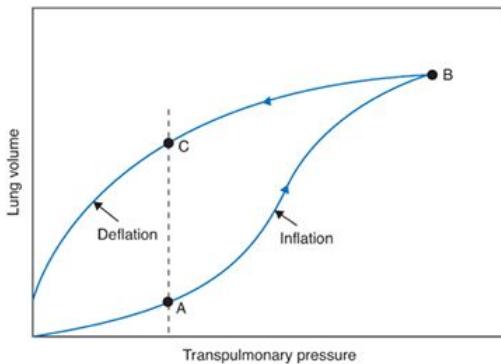


FIGURE 24.26 The pressure versus volume (PV) curve of the lung, often called the “compliance” curve. In this case, lung volume is plotted against transpulmonary pressure. Note that for the same pressure, the lung has a larger volume (ie, is more compliant) during deflation than during inflation, as represented by the distance between points A and C. This is due to hysteresis of the lung tissue and is present whether the curves are measured dynamically (during a continuous flow) or statically (during interrupted flow). For a dynamic PV curve, the distance AC will be greater than for a static curve due to the additive effects of airflow resistance. The point of maximum slope of the inspiratory curve (inflation arrow) normally corresponds to functional residual capacity (FRC). If the lung is inflated starting at FRC, the “lower inflection point” of the curve (point A) is not seen.

Resistance

Respiratory system resistance is a complex and important topic. It is important because, in the perioperative period, complications such as bronchospasm or secretions in an endotracheal tube or partial circuit obstruction will present primarily as increased resistance. It is complex because there are many types of resistance that contribute to the overall resistance of the respiratory system. When anesthesiologists think of respiratory resistance, they are mainly thinking of the nonelastic resistance to gas flow and they are primarily thinking of frictional airflow resistance. Nonelastic resistance is a major component of the work of breathing, and because it cannot be stored, it is lost and dissipated as heat. Nonelastic resistance also includes the resistance of lung and chest wall tissue to deformation and compression of intrathoracic gas. Elastic resistance is the recoil of the lung and chest wall, and because it is recovered during expiration, it does not contribute to the work of breathing.

Respiratory resistance (R_{RS}) is calculated as the pressure gradient divided by the inspiratory flow. During a constant flow situation such as volume-control ventilation, this would be calculated from [Figure 24.25](#) as

$$R_{RS} \text{ (cm H}_2\text{O/L per second)} = P_{\text{Peak}} - P_{\text{Plateau}} \text{ (cm H}_2\text{O)} / \text{inspiratory gas flow (L per second)}$$

However, normal spontaneous ventilation and pressure-control ventilation have variable flow rates and a mean gas-flow rate approximation is necessary to calculate respiratory resistance. Airflow resistance in normal healthy individuals breathing spontaneously is approximately 1 cm H₂O/L/second. This can increase to 5 to 10 cm H₂O/L/second in COPD and asthma.²⁰ Breathing through an 8-mm internal diameter endotracheal tube at a flow of 1 L/second creates a resistance of approximately 5 cm H₂O/L/second, and this increases to 8 cm H₂O/L/second for a 7-mm endotracheal tube.²¹

To quantitatively measure respiratory resistance in the operating room is not simple because it is difficult to separate respiratory system resistance from apparatus resistance. In the pulmonary function laboratory, this is done with plethysmography and a variety of flow-interrupter techniques. Fortunately, it is relatively simple to monitor changes in respiratory resistance in the operating room by following changes in dynamic compliance.

Gas flow during respiration is a mixture of turbulent and laminar flows and the turbulent/laminar interface moves in the air column during the respiratory cycle. Laminar flow occurs beyond the 11th-generation airways. Turbulent flow in the larger conducting airways aids clearing of secretions by coughing. In a healthy person, frictional airflow resistance is mainly due to larger airways: Mouth and pharynx 40%, larynx and large airways 40%, and small airways (<3 mm diameter) contribute 20%.²² However, changes in airflow resistance are most commonly due to changes in the caliber of the small airways. Small airway caliber can be decreased by contraction of smooth muscle in the airway wall or by compression (due to reversal of the normal transluminal pressure gradient in the collapsible distal airways).

Airway resistance is inversely proportional to lung volume and increases exponentially as the lung deflates below FRC. The application of PEEP or CPAP to patients who have a decreased FRC will benefit their respiration not only by raising their FRC above CC but also by decreasing their respiratory resistance, and thus their work of breathing, at a higher lung volume.

An increase in resistance to inspiration is detected by the muscle spindles in the diaphragm and leads to an increased force of contraction. This spinal reflex is preserved during anesthesia. In the awake patient, this reflex is augmented by a conscious cortical response that also increases the force of inspiration.²³ Increased expiratory resistance does not normally initiate a response if the resistance is <10 cm H₂O. The FRC is increased passively by the increased resistance until the increased elastic recoil balances the increased work of expiration. However, the ensuing increased intrathoracic pressure may decrease venous return and cardiac output. Patients tolerate increased airway resistance by increasing the work of breathing and in the short term will usually maintain a normal partial pressure of carbon dioxide (Paco₂). Eventually, a major increase in airway resistance may lead to respiratory muscle fatigue and the Paco₂ will start to rise. An elevated Paco₂ in a patient with increased respiratory resistance who has a normal baseline Paco₂ is an ominous sign of impending respiratory failure.

The Equal Pressure Point

Expiratory respiratory resistance will normally be lower than inspiratory resistance because the lung is at a larger volume at all stages of expiration than inspiration (see [Figure 24.26](#)). However, there are situations when expiratory resistance exceeds inspiratory resistance, these include the following: during a forced expiration (or cough) in a normal patient, during quiet breathing in some patients with severe emphysema (see the following text), and during forced expiration in some patients with an intrathoracic tracheal tumor or tracheobronchial compression from a mediastinal mass. In these instances, where expiratory resistance exceeds inspiratory resistance, the underlying cause is dynamic airway compression, which creates a moving flow limiting narrowing in the airway called the **equal pressure point** (EPP). In [Figure 24.27](#) at FRC before inspiration, ([Figure 24.27A](#)) airway pressure throughout is zero (no-flow situation) because the intrapleural (transpulmonary) pressure is -5 cm H₂O; there is a net +5 cm H₂O pressure distending the airways and alveoli. As inspiration begins, ([Figure 24.27B](#)) intrapleural and alveolar pressure falls by 3 cm H₂O and flow begins. Because of the pressure drop along the airway, the pressure will be negative in the airway but less than the alveolar pressure. This increases the distending pressure of the airways in this case from +5 to +6 cm H₂O. At end inspiration, ([Figure 24.27C](#)) the distending pressure in the no-flow condition is +8 cm H₂O and the pressure through the airway returns to zero. During quiet expiration, the recoil intrapleural pressure returns to -5 cm H₂O, and this creates a net pressure in the alveolus of +3 cm H₂O, which diminishes proximally as air flows out the tracheobronchial tree. The downstream distending pressure falls along the airway (represented by +6 cm H₂O in [Figure 24.27D](#)). Because this is a dynamic process, due to tissue resistance, the airway caliber will normally be larger at a given point for the same distending pressure during expiration than during inspiration. In a no-flow situation, the same distending pressure will result in equivalent airway diameters. During a forced expiration, ([Figure 24.27E](#)) the airway pressures increase (in this case by 24 cm H₂O, resulting in a net intrapleural pressure of +16 cm H₂O for same lung volume as [Figure 24.27C](#)) and a gradient is created along the expiratory air column. At the point where the intrapleural pressure equals the air column distending pressure (+16 cm H₂O), an EPP is created. The airway will narrow

proximal to this point (+15) to the thoracic outlet (+14). This becomes the flow-limiting point of expiration, and no amount of increased effort can increase the expiratory flow at a particular lung volume because the driving pressure is fixed by the difference between the alveolar and intrapleural pressures (8 cm H₂O in [Figure 24.27E](#)). This EPP allows the creation of a point of gas-flow acceleration and turbulence in the expiratory air column during normal coughing that has a Bernoulli effect (decreased lateral pressure in a region of increased flow velocity) to detach secretions from the tracheobronchial walls. During forced expiration, as lung volumes decrease and airway pressures decrease, intrapleural pressures are maintained and the EPP will move distally in the airway.²⁴

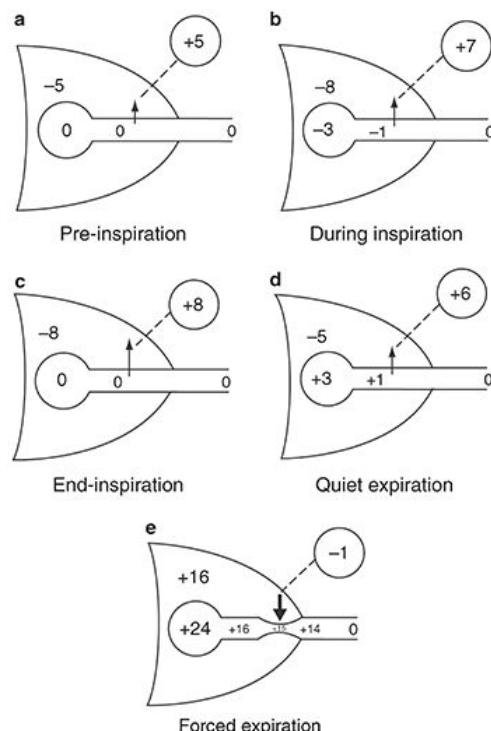


FIGURE 24.27 The effects of the intrapleural and alveolar pressures during quiet breathing (a-d) and the creation of an equal pressure point in the airway of a normal patient during forced expiration (e) (see text for details). Reprinted by permission from Springer: Ma M, Slinger P. Anesthesia for patients with end-stage lung disease. In: Slinger P, ed. Principles and Practice of Anesthesia for Thoracic Surgery. New York, NY: Springer; 2011:343-365. Figure 24.7. Copyright © 2011 Springer Science+Business Media, LLC.

During a maximal respiratory effort, the EPP is responsible for the difference in the shapes of the expiratory versus inspiratory limbs of the flow-volume curve ([Figure 24.28](#)). The linear portion of the expiratory flow, after the initial peak flow, is caused by the EPP. The peak flow is effort dependent, but the linear portion of the expiratory flow is effort independent (ie, no amount of increased expiratory effort at a given lung volume can increase the maximal flow rate at that volume). During quiet breathing, the inspiratory and expiratory limbs of the flow-volume curve are mirror images due to the absence of an EPP. In the range of lung volumes used during quiet breathing, both inspiratory and expiratory flow normally can be increased approximately threefold by maximal effort if needed.

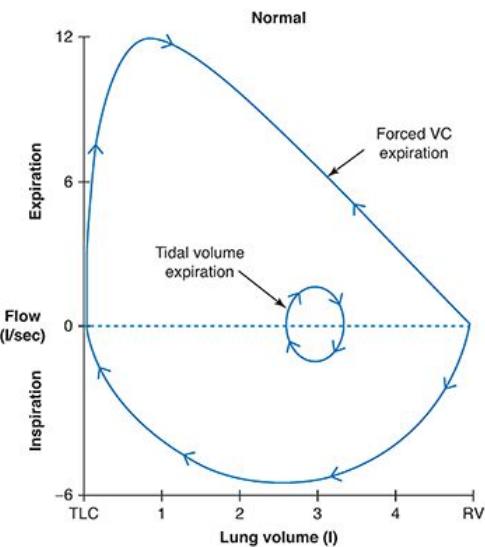


FIGURE 24.28 The airflow versus lung volume plot during maximal force inspiration and expiration of a normal individual (outer curve) from residual volume (RV) to total lung capacity (TLC). The inner elliptical curve “tidal volume” is during normal quiet breathing. During maximal inspiration, the curve is hyperbolic. During maximal expiration (forced vital capacity [VC] expiration), after the initial peak, the curve becomes linear due to the formation of an equal pressure point in the airway.

Work of Breathing

Work is the product of $force \times distance$ or $pressure \times volume$. Technically, **work** is calculated for a single event. However, the term **work of breathing** is commonly used to denote the ongoing energy expenditure required by the respiratory system. During normal quiet breathing, expiration is passive and does not require work. Half of the work of inspiration is stored in the deformation of the muscles of inspiration and the lung tissue. This potential energy provides the work necessary for expiration. The other half of the work of inspiration is dissipated as heat in overcoming the frictional forces of tissue and gas movement. The oxygen requirement for the work of breathing is less than 2% of the normal basal oxygen consumption (3-4 mL/kg/minute). In healthy individuals, the oxygen consumption of the muscles of respiration does not become important until rates of respiration approaching maximal minute ventilation (60-80 L/minute; ie, 15 \times basal ventilation) are reached. However, in patients with COPD, due to the mechanical inefficiency of the respiratory system, increasing the minute ventilation to 20 L/minute may increase the oxygen consumption of the muscles of respiration to levels of 200 mL/minute.²⁵

The work performed against the elastic resistance of the lung and chest wall increases proportionally when breathing is slow and deep. Conversely, the work performed against airflow resistance increases when breathing is rapid and shallow. Each individual will have an optimal rate and tidal volume that minimizes the work of breathing depending on the compliance and resistance of his or her respiratory system. At rest, he or she will normally breathe at a rate that minimizes the oxygen consumption required for gas exchange. For normal adults, this usually corresponds to a resting respiratory rate of 15 to 16 breaths per minute. For patients with obstructive diseases, this rate will usually tend to be lower and higher for patients with restrictive lung diseases.⁹

Although the work of breathing is minimal for healthy individuals, it may represent a significant challenge for a patient with respiratory or cardiac failure who has diminished reserves. This always needs to be considered when weaning such a patient from mechanically assisted ventilation.

Respiratory Fatigue

Fatigue of the respiratory system may occur at any point from the central nervous system (CNS) to the muscles of respiration. The diaphragm is possibly the most fatigue-resistant skeletal muscle and can sustain

resistive loads of up to 40% of maximal indefinitely. However, fatigue will occur with loads exceeding 40%. Because the oxygen supply requirement for the diaphragm is high in proportion to its mass, it is susceptible to hypoxia either due to decreased oxygen content of the arterial blood or due to decreased cardiac output.²⁶ The diaphragm can be rested for a short period by mechanical ventilation, but histologic evidence of muscle fiber atrophy can be seen after as little as 18 hours of mechanical ventilation, and clinical evidence of weakness is seen within days.²⁷ Ventilator-induced diaphragm dysfunction is characterized by atrophy of both type I and II fibers, with altered gene expression leading to an increase in proteolysis.²⁸

Physiology of Ventilation and Perfusion

Initially, it is a difficult concept to grasp, but ventilation is preferentially distributed to the smaller alveoli close to the middle and lower portion of the lungs rather than to the larger alveoli in the more superior lung regions. This is because the lower alveoli are at a steeper portion of their compliance curve (see **Figure 24.15**). The most frequent explanation for this nonuniformity is the effect of gravity on the lung parenchyma. In the upright posture, the greatest vertical height is attained by the lung. The tendency for the lung to retract away from the chest wall at its apex creates a more negative (subatmospheric) pleural pressure than the pleural pressure at the lower dependent portions of the lung where its weight reduces the magnitude of the negative pleural pressure. The gradient of pleural pressure from the lung apex to its base has been estimated at 0.4 cm H₂O per each centimeter of vertical height. Obviously, one might expect less of a transpulmonary pressure gradient from nondependent to dependent portions of the lung when supine or prone as compared to the upright position. In the upright individual, during a spontaneous breath, inspired gas will tend to preferentially enter those open alveoli near the base of the lung, which are the most compliant. As the breath continues, the gas will enter the more apical, less compliant alveoli and any previously atelectatic basilar alveoli as they become recruited by the traction exerted by the remainder of the expanding lung. Also, the rate of inspiration directly impacts the homogeneity of gas distribution. At high inspiratory rates, air is distributed more evenly throughout the lung than at very slow rates.²⁹

Pulmonary Circulation

The lung circulation is composed of two sources of blood flow: the pulmonary circulation from the main pulmonary artery and the smaller bronchial circulation arising from the aorta. The pulmonary circulation dominates, by volume, and serves to deliver the mixed venous blood to the alveolar capillaries to facilitate gas exchange and to act as a large, low-resistance reservoir for the entire cardiac output from the right ventricle. The bronchial circulation serves to provide nutritional support to the airways and their associated pulmonary blood vessels.³⁰ The bronchial circulation also provides a constant source of heat and moisture for warming and humidifying the inspired air.

Pulmonary Hemodynamics

Despite receiving all of the cardiac output from the right ventricle, the pulmonary vasculature maintains a relatively low pulmonary blood pressure. The normal adult mean pulmonary artery pressure (P_{PA}) is 9 to 16 mm Hg with systolic P_{PA} of 18 to 25 mm Hg. Several features enable the pulmonary circulation to maintain this high flow at such low pressures. First, the pulmonary vasculature is extremely thin walled with far less arterial vascular smooth muscle than its systemic counterparts. The result is a highly compliant reservoir capable of accommodating an average 3.2 L/minute/m² blood flow at rest or 6 to 8 times that flow during exercise. Second, the total PVR is quite low, on the order of less than 250 dyne•s/cm⁵. This minimizes the pressure work faced by the less robust right ventricle while still enabling the right ventricle to match the output of the left ventricle. The PVR can change as a result of numerous factors, hypoxia, acidosis, mitral valve stenosis or regurgitation, left ventricular failure, primary pulmonary hypertension, or pulmonary emboli, to name just a few. The PVR can be calculated using data from a pulmonary artery catheter as

$$\text{PVR} = [(P_{PA} - PAOP) / CO] \times 79.9$$

where PAOP is the pulmonary artery catheter occlusion pressure, which is assumed to reflect the left atrial pressure, CO is cardiac output (L/minute), and the factor, 79.9 converts from mm Hg/L/minute to units of absolute resistance ($\text{dyne}\cdot\text{s}/\text{cm}^5$).

Distribution of Perfusion

There is a gradient of distribution of perfusion of the lung that is similar but not identical to the gradient of distribution of ventilation, with increased perfusion of regions in the central and lower regions compared to the upper regions. This perfusion gradient depends in part on the architecture of the lung and the resistance of the pulmonary vessels, which varies with lung volume and is lowest in the regions of the lung closest to FRC (Figure 24.29). Gravity, posture, and alveolar pressure will also have effects on the distribution of pulmonary blood flow.³¹

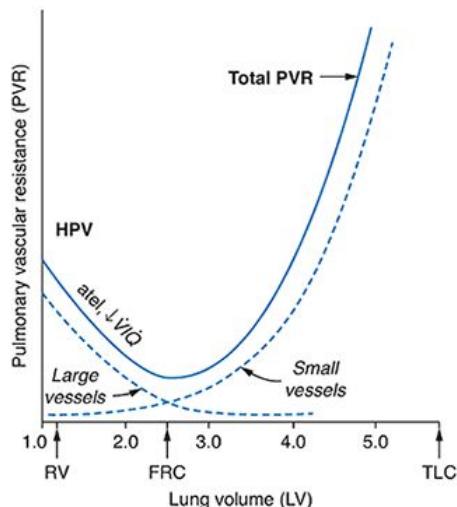


FIGURE 24.29 The relationship between pulmonary vascular resistance (PVR) and lung volume. The PVR is lowest at functional residual capacity (FRC) and increases as the lung volume decreases toward residual volume (RV), owing primarily to the increase in resistance of large pulmonary vessels. The PVR also increases as lung volume increases above FRC toward total lung capacity (TLC) because of an increase in resistance of small interalveolar lung vessels. Abbreviation: atel, atelectasis; HPV, hypoxic pulmonary vasoconstriction; V/Q, ventilation/perfusion.

Matching of Ventilation and Perfusion

Within certain limits, the lung attempts to match ventilation to perfusion. However, the matching is never ideal because the ventilation and perfusion gradients are not identical (Figure 24.30). This matching is closer during spontaneous ventilation than during positive pressure ventilation. With positive pressure ventilation, the effects of alveolar pressure are increased and pulmonary blood flow distribution becomes less homogeneous. This led to the concept of perfusion zones of the lung as described by West et al³² (Figure 24.31A). In this concept, zone 1 (apical) is a region where alveolar pressure (P_A) exceeds both P_{PA} and pulmonary venous pressure (P_{PV}); hence, this ventilated lung region has no perfusion. In zone 2 (transitional), P_{PA} exceeds P_A , which exceeds P_{PV} with partial limitation of pulmonary blood flow. In zone 3 (basilar), $P_{PA} > P_{PV} > P_A$, so there is unrestricted pulmonary blood flow. In zone 4 (atelectatic), a region of lung collapse, $P_{PA} >$ pulmonary interstitial fluid pressure (P_{ISF}) $> P_{PV} > P_A$, so again, there is a limitation of pulmonary blood flow depending on the tissue pressure in the region of collapse. Although West's zones have been a useful concept to emphasize the effects of airway and alveolar pressure on pulmonary blood flow, these zones are an oversimplification. First, because alveolar pressure does not remain constant but varies throughout the respiratory cycle, more so during positive pressure than controlled ventilation. Thus, the boundaries between

these zones are constantly moving. Also, it has been demonstrated by perfusion scanning that the distribution of blood flow in the lung is not actually in layers (like a cake) but in concentric spheres (like an onion) ([Figure 24.31B](#)).

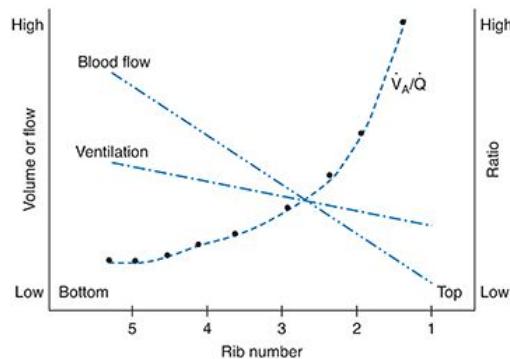


FIGURE 24.30 Distribution of blood flow (perfusion) and alveolar ventilation and the ventilation-to-perfusion ratio (VA/Q) as a function of the distance from the base of the lung (to the left in the figure) to the apex (to the right). In the upright position, both ventilation and blood flow are greater at the base of the lung than at the apex. However, the gradient is steeper for blood flow than ventilation. Thus, the VA/Q ratio is higher at the apex than in the mid or dependent lung regions. *Reprinted by permission from Springer: Jaeger JM, Blank RS. Essential anatomy and physiology of the respiratory system and the pulmonary circulation. In: Slinger P, ed. Principles and Practice of Anesthesia for Thoracic Surgery. New York, NY: Springer; 2011:51-69. Figure 4.6. Copyright © 2011 Springer Science+Business Media, LLC.*

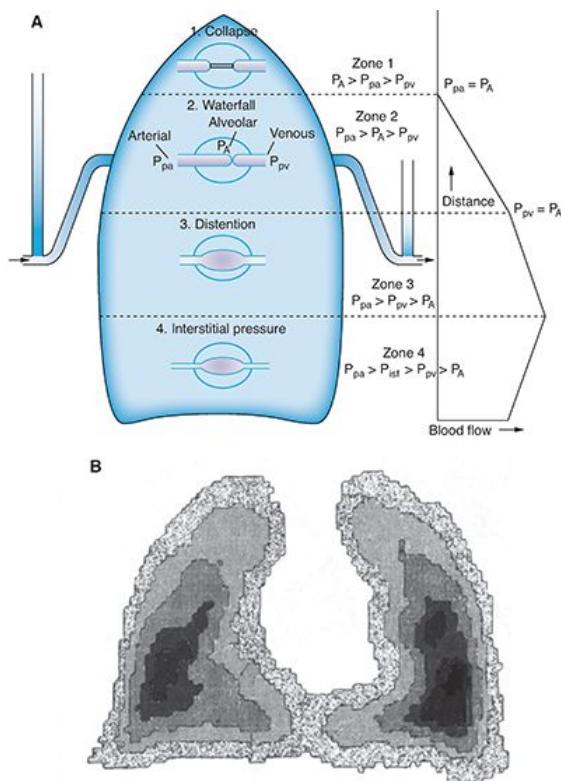


FIGURE 24.31 The distribution of pulmonary blood flow in the upright position. A, Pulmonary blood flow as affected by gravity and alveolar pressure. This classic description based on the work of West et al³² divides pulmonary blood flow into four zones: P_A , alveolar pressure; P_{pa} , pulmonary artery pressure; P_{pv} , pulmonary

venous pressure, P_{if} , pulmonary interstitial fluid pressure. B, Subsequent investigations with lung scanning have shown that blood flow is actually distributed more in a central to peripheral pattern. *Reproduced with permission from Slinger P, ed. Principles and Practice of Anesthesia for Thoracic Surgery. New York, NY: Springer; 2011.*

Due to the combined effects of the architecture of the lung parenchyma and vasculature and gravity, there is a matching of ventilation and perfusion (VA/Q) in the lung. Typical resting values in an adult are 4 and 5 L/minute for alveolar ventilation and cardiac output for a VA/Q ratio of 0.8. As can be seen from [Figure 24.32](#), this VA/Q matching is optimal in central lung regions but becomes unequal at the apex and base of the lung. Positive pressure ventilation, decreased cardiac output, atelectasis, and many disease states will further interfere with normal VA/Q matching.

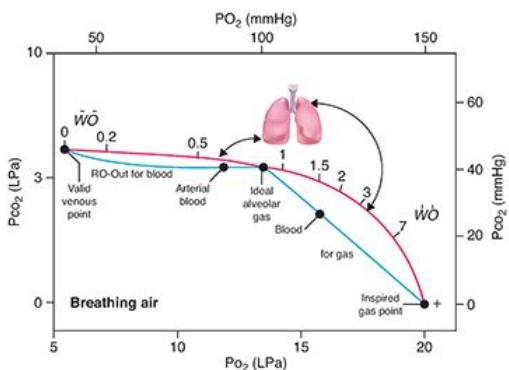


FIGURE 24.32 The heavy line indicated all possible values of alveolar Po_2 and PCO_2 with ventilation/perfusion ratios ranging from zero (to the left, lung base) to infinity (to the right, lung apex) for a person breathing air. Mixed expired gas is a mixture of ideal alveolar gas and dead space. Arterial blood is a mixture of blood with the same gas tensions as ideal alveolar gas and shunt (mixed venous blood).

Dead Space

Like many concepts in respiratory physiology, dead space is crucially important in clinical practice and deceptively simple on the surface but actually extremely complex. Any portion of an inspired breath, which does not enter gas exchanging lung units, is dead space. Minute ventilation (VE) is the sum of alveolar ventilation (VA) and dead space ventilation (VD):

$$V_E = V_A + V_D$$

Dead space can be subdivided into two primary components: physiologic dead space and apparatus dead space. Apparatus dead space will only apply to patients attached to a breathing circuit. Physiologic dead space is further subdivided into airway dead space and alveolar dead space ([Figure 24.33](#)). The airway dead space is the portion of a breath that goes to the mouth, pharynx, and tracheobronchial tree but does not enter the alveoli. Airway dead space is also called **anatomic** dead space by some authors, but this latter is a confusing term. Alveolar dead space is the portion of a breath that enters alveoli, which are ventilated but not perfused (ie, West's zone 1).

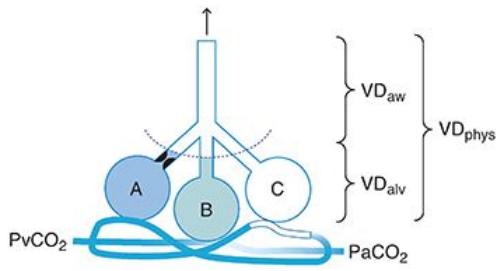


FIGURE 24.33 A simplified three-compartment model of the lung with A representing shunt; B, an ideal gas unit; and C, alveolar dead space (VD_{alv}). Physiologic dead space (VD_{phys}) is filled with air containing no carbon dioxide, shown as the white area. The VD_{phys} is the sum of airway dead space (VD_{aw}) and VD_{alv} . The airway-alveolar interface is demonstrated by the dotted line. Abbreviation: $PvCO_2$, venous PCO_2 . Reprinted with permission from Tusman G, Sipmann FS, Bohm SH. Rationale of dead space measurement by volumetric capnography. Anesth Analg. 2012;114(4):866-874. Copyright © 2012 International Anesthesia Research Society.

Airway dead space is relatively constant. However, it does vary directly with lung volume and bronchodilation increases airway dead space. As tidal volume (VT) decreases, the portion of each breath that is dead space (VD/VT) ratio will increase. Airway dead space will decrease slightly, at lower lung volumes, but not enough to compensate for the fall in VT. Airway dead space is decreased by endotracheal intubation because much of the mouth and pharynx dead space is bypassed. However, the net effect on total dead space will depend on the additional equipment dead space of the circuit attached to the patient. For most correctly functioning modern anesthetic apparatus, equipment dead space is not clinically important.

A healthy person, breathing spontaneously, will have practically no alveolar dead space. Tidal volume breathing will usually result in a VD/VT of approximately 0.3, entirely due to airway dead space. Alveolar dead space, however, becomes clinically important during positive pressure ventilation and in any condition of altered hemodynamics. Decreased cardiac output, pulmonary embolism, and changes in posture will all have clinically important effects on alveolar dead space, usually by increasing zone 1. These three components, apparatus, airway, and alveolar, make up the total dead space.

Measurement of Dead Space

The measurement of dead space was described initially by Bohr.³³ Mixed expired gas is collected, and carbon dioxide (CO_2) analyzed to give a mean expired CO_2 tension ($PECO_2$) and the arterial blood gas ($Paco_2$) sampled. The Bohr equation is

$$V_D/V_T = (Paco_2 - PECO_2) / Paco_2$$

The derived VD/VT can be applied to minute ventilation or to a single breath. In a healthy person breathing spontaneously, because the alveolar dead space is very small, the end-tidal CO_2 tension ($PETCO_2$) can be substituted for $Paco_2$ in the Bohr equation to measure dead space. In the ventilated patient, alveolar dead space is often clinically significant, and the absolute number calculated for dead space with this calculation will be falsely low. Similarly, $PETCO_2$ can be substituted for $PECO_2$ to give an estimate of the alveolar dead space for a ventilated patient. This calculation is crude as an absolute measurement; however, the gradient $Paco_2$ - $PETCO_2$ is clinically an extremely useful trend. It is uncommon for airway dead space to change during the course of an anesthetic, so any increase in the $Paco_2$ - $PETCO_2$ gradient is most likely due to an increase in alveolar dead space. The $Paco_2$ is inversely related to the V_A :

$$Paco_2 = (VCO_2 / V_A) \times K$$

Where VCO_2 is the total body production of CO_2 and VA is the alveolar ventilation and K is a constant. Because the patient's metabolic rate is usually constant during anesthesia (if body temperature is maintained), VCO_2 is relatively constant. Changes of minute ventilation (tidal volume \times respiratory rate) will usually cause a direct and inverse change in the $Paco_2$. However, this equation uses VA , not minute ventilation. If the dead space increases (eg, decreased cardiac output) and minute ventilation is unchanged, VA will decrease and $Paco_2$ will rise.

Ventilation monitoring during anesthesia includes monitoring of expired CO_2 . This is usually presented as time-based capnography. Volume-based capnography is similar but may allow for more accurate measurement of dead space and CO_2 production ([Figure 24.34](#)).³⁴

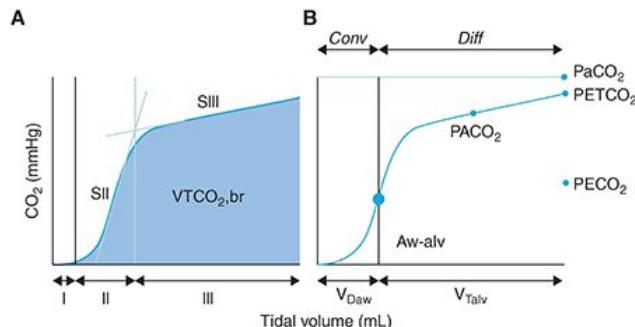


FIGURE 24.34 Capnometry. Expired carbon dioxide (CO_2) tension plotted here against tidal volume. The CO_2 is most commonly displayed plotted against time. Integration of the expired gas flow and CO_2 signals allows calculation of CO_2 production (volume of expired CO_2 per breath [$VTCO_2$, br]). The expired CO_2 curve has three phases (I, II, III) and two slopes (SII and SIII). Airway dead space (V_{Daw}) can be measured from the midpoint of SII, the airway-alveolar (Aw-alv) gas interface. The slope of SIII increases with increased inequality of regional ventilation in the lung. Abbreviations: Conv, convection; Diff, diffusion; $PACO_2$, mean alveolar PCO_2 ; $PECO_2$, mixed expired PCO_2 ; $PETCO_2$, end-tidal PCO_2 ; V_{Talv} , alveolar tidal volume. *Reprinted with permission from Tusman G, Sipmann FS, Bohm SH. Rationale of dead space measurement by volumetric capnography. Anesth Analg. 2012;114(4):866-874. Copyright © 2012 International Anesthesia Research Society.*

Shunt

Shunt or venous admixture is the portion of the venous blood returned to the heart that passes to the arterial circulation without being exposed to normally ventilated lung units. There are two major subdivisions of shunt: extrapulmonary and pulmonary. Extrapulmonary shunt is venous blood that does not pass through the lungs. There are two normal sources of this shunt: the thebesian veins in the left heart and the bronchial circulation. These normally represent <1% of the total cardiac output. Abnormal types of extrapulmonary shunt include congenital cardiac defects with right-left communications.

Pulmonary shunt is venous blood passing through lung regions with decreased or no V_A . [A in Figure 24.33](#) is an illustration of this concept in which shunt and dead space seem to be unrelated. However, like so much in respiratory physiology, [Figure 24.33](#) is an oversimplification. Shunt and dead space are the extremes of the continuum of ventilation and perfusion matching (see [Figure 24.33](#)). Shunt has a large effect on Pao_2 but a limited effect on $Paco_2$. Shunt is the commonest cause of hypoxemia during anesthesia. Other causes are a low alveolar oxygen tension (eg, hypoventilation or a low inspired oxygen concentration [FIO_2]) or a decreased mixed venous oxygen content (eg, low cardiac output) ([Figure 24.35](#)). The fraction of total cardiac output (Q_T) that is shunt (Q_S) can be calculated from the arterial (Cao_2), pulmonary end-capillary ($Cc' O_2$), and mixed venous (pulmonary arterial) (Cvo_2) oxygen contents. Calculation of blood oxygen contents are discussed as follows.

$$Q_S/Q_T = Cc'_{O_2} - Ca_{O_2} / Cc'_{O_2} - Cv_{O_2}$$

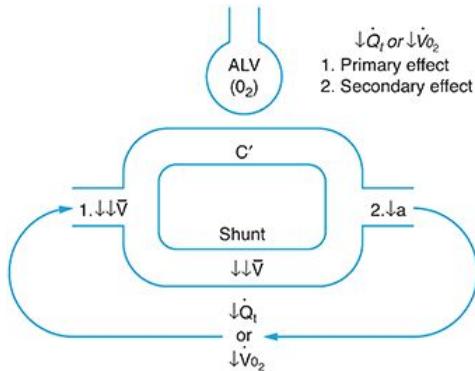


FIGURE 24.35 A simplified diagram of the effects of a decrease in mixed venous oxygen saturation (v) on arterial oxygenation (a). Mixed venous blood passes either through ventilated lung regions (ALV), where it is oxygenated in the pulmonary capillaries (C'), or through nonventilated (Shunt) lung regions. A decrease in mixed venous oxygen due to either a decrease in cardiac output (\dot{Q}_t) or an increase in oxygen consumption (\dot{V}_{O_2}) will pass through the pulmonary shunt and result in a fall in arterial oxygenation. *Reprinted from Lumb AB. Nunn's Applied Respiratory Physiology. 7th ed. Edinburgh: Churchill Livingstone/Elsevier; 2010. Copyright © 2010 Elsevier. With permission.*

This can be remembered as the little step in oxygenation in [Figure 24.35](#) ($Cc'_{O_2} - Ca_{O_2}$) divided by the big step in oxygenation ($Cc'_{O_2} - Cv_{O_2}$), so normally the shunt fraction (Q_S/Q_T) will be very small (<.05).

Alveolar-Arterial Oxygen Difference (A-aDO₂)

Although the concept of shunt is extremely important and useful in anesthesia, it is uncommon to actually calculate the shunt fraction in patients. Similar to the calculation of the PaCO_2 - ETCO_2 gradient as a monitor of changes in dead space, the gradient of PAO_2 to Pao_2 tension ($A-a\text{DO}_2$) can be used as a crude monitor of shunt. The $A-a\text{DO}_2$ gradient is proportional to shunt, but the absolute gradient increases as FIO_2 increases. However, if FIO_2 and mixed venous PO_2 (Pv_{O_2}) (ie, cardiac output and temperature) remain relatively constant, the trend of the $A-a\text{DO}_2$ is a reasonably reliable monitor of changes in shunt. The PAO_2 is calculated from the theoretical “ideal” alveolar gas equation:

$$\text{PAO}_2 = \text{PiO}_2 - \text{Paco}_2 / \text{RQ}$$

Because the volume of CO_2 produced is normally less than the volume of oxygen consumed, the Paco_2 cannot be substituted directly into the equation. In order to estimate the actual tension of oxygen in the ideal alveolus, the Paco_2 is divided by the respiratory quotient (RQ).

The RQ (CO_2 production / oxygen consumption) is a dimensionless number, which varies according to which substance is being consumed for fuel by the body. For carbohydrates, the approximate RQ = 1.0; for proteins, 0.9 to 0.8; and for fats, 0.7. A mixed value for RQ of 0.8 is commonly used in this equation.

The inspired PO_2 (PiO_2) depends on the fractional concentration of inspired oxygen (FIO_2) and the barometric pressure (P_B) minus the saturated pressure of water vapor in the alveolus (P_{H2O}), which is 47 mm Hg:

$$\text{PiO}_2 = \text{FIO}_2 \times (P_B - P_{H2O})$$

So, the combined alveolar gas equation becomes

$$PAO_2 = [FIO_2 \times (P_B - P_{H2O})] - Paco_2 / RQ$$

For a person breathing air ($FIO_2 = 0.21$) at sea level (approximately $P_B = 760$ mm Hg) with a $Paco_2$ of 40 mm Hg, the ideal alveolar PO_2 calculation would be

$$PAO_2 = [0.21 \times (760 - 47)] - (40 / 0.8) = 100 \text{ mm Hg}$$

This is a simplified version of the equation, which does not compensate for differences in the inspired and expired tidal volumes but is clinically useful for rapid calculation of the A-aDO₂.

Hypoxic Pulmonary Vasoconstriction

The lung has a unique reflex to try and minimize these perturbations in VA/Q matching. This reflex is HPV. The pulmonary arterioles are unique in that they will respond to regional hypoxemia by constricting.³⁵ The arterioles in essentially all other tissues in the body vasodilate in response to hypoxemia. This reflex will tend to redirect blood flow from poorly or nonventilated lung regions to better ventilated regions. The primary stimulus for HPV is alveolar hypoxia. The HPV begins within seconds and is biphasic with most of the rapid-phase response complete within 20 minutes. A slower phase begins after approximately 40 minutes and continues to increase over many hours (Figure 24.36).³⁶ Of note, once the slow phase of HPV has started, the resolution of HPV will also be delayed. This has important implications for bilateral thoracic surgery cases involving sequential periods of alternating one-lung ventilation (OLV).

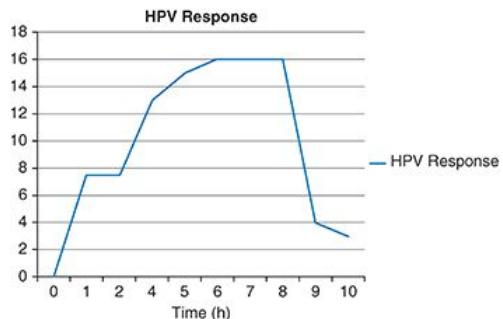


FIGURE 24.36 The relationship between hypoxic pulmonary vasoconstriction (HPV) (vertical axis) and time in hours (horizontal axis) in humans exposed to isocapnic hypoxia (approximate inspired PO_2 60 mm Hg), beginning at 0 hour with a return to normoxia at 8 hour. The HPV response was measured as the increase in echocardiographic right ventricular systolic pressure. Note the two-phase, rapid and slow, onset of HPV. Also note that after prolonged HPV, the pulmonary pressures do not return to baseline for several hours. *Based on data from Talbot NP, Balanos GM, Dorrington KL, et al. Two temporal components within the human pulmonary vascular response to 2 h of isocapnic hypoxia. J Appl Physiol (1985). 2005;98:1125-1139.*

A low PvO_2 , and therefore low pulmonary artery PO_2 , will augment the HPV response to a hypoxic FIO_2 , but low PvO_2 alone has no effect.³⁷ As the size of the hypoxic lung segment increases, PVR increases, mixed venous oxygen tensions begin to fall, and the ability of HPV to shunt blood to the remaining well-ventilated lung becomes compromised. The HPV remains intact despite chemical sympathectomy, bilateral vagotomy, and denervation of the carotid and aortic chemoreceptors.³⁸ Bilateral lung transplant recipients retain their hypoxic pulmonary vasoconstrictive responses.³⁹ The HPV is augmented by conditions and chemicals, which globally enhance PVR such as acidemia, hypercapnia, histamine, serotonin, and angiotensin II.

The actual cellular oxygen sensor for HPV has yet to be determined. Current research implicates the mitochondria of the pulmonary vascular smooth muscle cell as the main site. Numerous biochemical studies have indicated that selective interruption of the mitochondrial electron transport chain complexes can impair HPV. A unifying theme seems to be the hypoxia-induced change in the level of oxygen free radicals and hydrogen peroxide in the smooth muscle cell. These changes affect the release of calcium from the

sarcoplasmic reticulum and the voltage-dependent membrane conductance to potassium resulting in depolarization and contraction of the smooth muscle, hence vasoconstriction.⁴⁰ The response may involve decreased production of nitric oxide by the pulmonary epithelium and endothelium.⁴¹

Movement of Gas

Oxygen Transport

Oxygen diffuses into the plasma of the pulmonary capillary blood, driven by its concentration gradient from the alveoli. This oxygen is then taken up by partially desaturated hemoglobin (Hb) molecules in the red blood cells of mixed venous blood to form oxyhemoglobin. Due to the high affinity of Hb for oxygen, a large proportion (normally >98%) of the total oxygen in arterial blood is carried within the red blood cells as oxyhemoglobin. Less than 2% is circulated as dissolved oxygen. However, it is actually the tension of the oxygen dissolved in plasma (PaO_2) that is measured in an arterial (or venous [Pvo_2]) blood gas sample. There is a dynamic equilibrium between the oxygen dissolved in plasma and that bound to Hb within the red blood cells. The quantity of oxygen dissolved in blood is directly proportional to its partial pressure. For each mm Hg of PO_2 , there is 0.003 mL of dissolved oxygen per 100 mL of blood. Thus, for a PaO_2 of 100 mm Hg, there will be 0.3 mL of dissolved oxygen in 100 mL of blood. This compares to approximately 20 mL of oxygen bound to Hb in the red cells and is usually not of clinical importance. However, this dissolved oxygen can approach 1.5 mL with an FIO_2 of 1.0 and can be clinically even more important in hyperbaric environments.

Normal adult hemoglobin (HbA) is a four-protein molecule with two α chains and two β chains. Each protein chain is attached to one heme unit ([Figure 24.37](#)). Heme is an iron-porphyrin complex capable of reversible binding to one oxygen molecule at its ferrous (Fe^{++}) atom. As each of the four heme units binds an oxygen molecule, it causes a change in the shape of the Hb molecule, which, in turn, causes the other heme units to be more exposed. The result is that each successive oxygen molecule is bound less (or more) tightly and released more (or less) easily. So, the release of oxygen by Hb as the PO_2 in the surrounding plasma falls (and conversely the uptake of oxygen by Hb as the PO_2 rises) is not in a linear correlation with PO_2 but curvilinear producing the oxyhemoglobin saturation curve (or dissociation curve) ([Figure 24.38](#)).

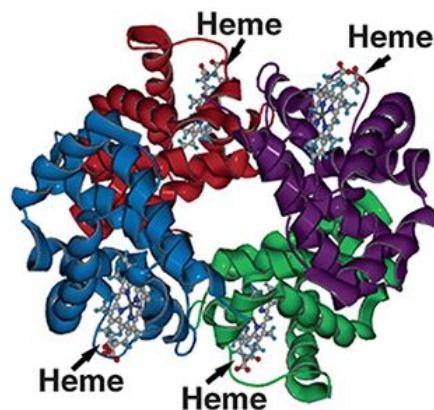


FIGURE 24.37 An oxyhemoglobin molecule is composed of two paired proteins. For hemoglobin A, these are two α chains and two β chains. Each globin chain is bound to a heme group capable of binding a single oxygen molecule.

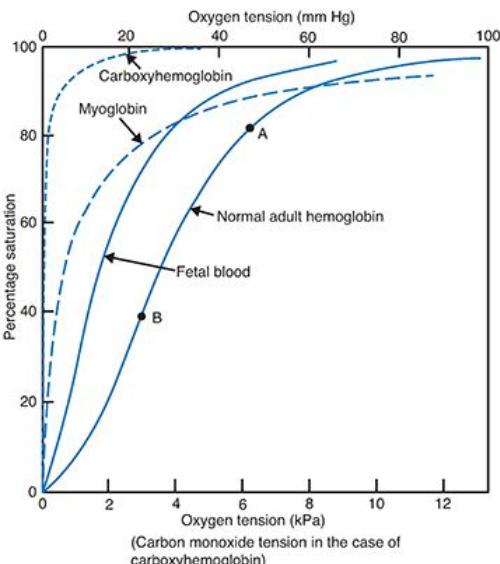


FIGURE 24.38 Dissociation curves of normal adult (HbA) and fetal (HbF) hemoglobin. Curves for myoglobin and carboxyhemoglobin are shown for comparison.

The PO_2 values of 40, 50, and 60 will correspond (approximately) to saturations of 70%, 80%, and 90%, respectively.

The oxygen content of blood can be calculated if the Pao_2 , the concentration of Hb in the blood, and the percentage saturation of Hb is known. Pure oxyhemoglobin will contain 1.39 mL/g. The saturation of the Hb in a blood sample is measured spectrophotometrically by comparing the absorption of two different wavelengths of near infrared light; one wavelength at which oxyhemoglobin and deoxyhemoglobin have approximately the same absorbance (typically 940 nm) and one at which they differ widely (typically 660 nm). Pulse oximetry uses the same principle but corrects for the peak arterial phase of a capillary blood flow by subtracting for the baseline venous flow absorption. Modern rapid blood gas analyzers often estimate oxygen saturation based on measured PO_2 and standard oxyhemoglobin (HbO_2) curves corrected for pH.

$$\text{The content of oxygen in blood} = \text{dissolved O}_2 + \text{O}_2 \text{ bound as HbO}_2$$

$$\text{For } 100 \text{ mL blood} = (\text{PO}_2 \times 0.003) + (\text{Hb concentration} \times \text{saturation}/100 \times 1.39)$$

For a patient with an Hb of 15 g/dL a PO_2 of 100 and saturation of 99% the blood, oxygen content would be $= (100 \times 0.003) + (15 \times 0.99 \times 1.39) = 0.3 + 20.6 = 20.9 \text{ mL oxygen}/100 \text{ mL blood}$. Mixed venous blood commonly has a saturation of approximately 70% and thus an oxygen content of 15 mL/100 mL.

Shifts of the Oxyhemoglobin Dissociation Curve

There are multiple different normal and abnormal variants of the Hb molecule. Each of these different Hb molecules has a different oxyhemoglobin dissociation curve (see [Figure 24.38](#)). By convention, to compare these curves, the PO_2 at the point of 50% saturation (P_{50}) is used as a reference. For HbA, the P_{50} is 26 mm Hg. Fetal hemoglobin (HbF) has two α chains and four γ chains. It is the major form of Hb present at birth and is replaced by HbA over the first 6 months of life. The HbF has a P_{50} of 19, so it is “left shifted” from HbA. Because its affinity for oxygen is stronger than HbA, oxygen is preferentially drawn from the mother’s blood to that of the fetus.

Carboxyhemoglobin is an abnormal Hb formed when carbon monoxide binds with heme. Carbon monoxide displaces oxygen from heme, and it shifts the oxyhemoglobin curve to the extreme left so that oxygen is not released to the tissues and cellular hypoxia results. The Fe^{++} atom in heme can be oxidized to

Fe^{+++} by a variety of drugs and chemicals such as nitrates. This forms a type of Hb called methemoglobin and will not bind oxygen.

The normal HbA oxygen saturation curve shifts to the left or right secondary to a variety of physiologic changes. An increase in hydrogen ion (H^+) concentration (ie, a decrease in serum pH), an increase in body temperature (T) and an increase in 2,3-diphosphoglycerate (DPG) shift the curve to the right. The 2,3-DPG is a compound normally present in red blood cells that tends to decrease the affinity of Hb for oxygen. It is increased by exposure to a low environmental oxygen (eg, at altitude) or in anemia. This can be remembered as DPG, H^+ , and T shift the Hb oxygen saturation curve to the right (riGHT). And their converses (decrease DPG, alkalosis, hypothermia) shift the curve to the left. In most situations of physiologic stress (ie, hypercarbia, acidosis, etc), it is advantageous to have the oxyhemoglobin curve shifted to the right and to increase oxygen unloading to the tissues.

There is normally no significant oxygen storage capacity in the body. This is unlike CO_2 , which has large stores in the body (see the following text). Oxygen is like rocket fuel and can be toxic to tissues in excess over a prolonged period. An average-size adult's oxygen consumption is approximately 250 mL/minute. The total content of oxygen in the blood will be approximately 700 to 800 mL and in the FRC 500 mL (breathing air). Tissue hypoxia will begin very quickly if the oxygen supply is cut off. Washing out the FRC with an FIO_2 of 1.0 can potentially provide a reserve of 2,500 mL of oxygen, a supply adequate for several minutes of apnea.

Carbon Dioxide Transport

The CO_2 is the main product of aerobic metabolism of proteins, fats, and carbohydrates. The CO_2 is moderately soluble in all body fluids (approximately 20 times more soluble than oxygen) and diffuses down its concentration gradient from its site of intracellular production into the capillary and venous blood. Similar to oxygen, the tension of dissolved CO_2 in blood is the portion measured in blood gas analysis. As can be seen in [**Figure 24.39**](#), CO_2 transport is like an upside-down iceberg with the dissolved CO_2 as the only visible portion. But, this is only a small proportion of the total CO_2 in the blood. The majority of CO_2 is transformed to bicarbonate ion (HCO_3^-) in the following reaction:



The first step of this reaction is slow in plasma but progresses rapidly in the presence of the enzyme carbonic anhydrase, which is present in red blood cells. The majority of CO_2 in the blood follow this pathway and is transported in the blood as HCO_3^- after diffusion into red cells and enzymatic conversion ([**Figure 24.40**](#)). A small portion of the CO_2 is transported in the blood combined to Hb as carbamino compounds. Blood with lower oxyhemoglobin saturation (ie, venous blood) is capable of carrying more CO_2 than blood with well-saturated Hb (ie, arterial). This is known as the Haldane effect. The Haldane effect is complicated and involves both increased carbamino- CO_2 carrying by desaturated Hb and also increased buffering of intracellular H^+ by deoxygenated Hb, which is less acidic than oxygenated Hb.

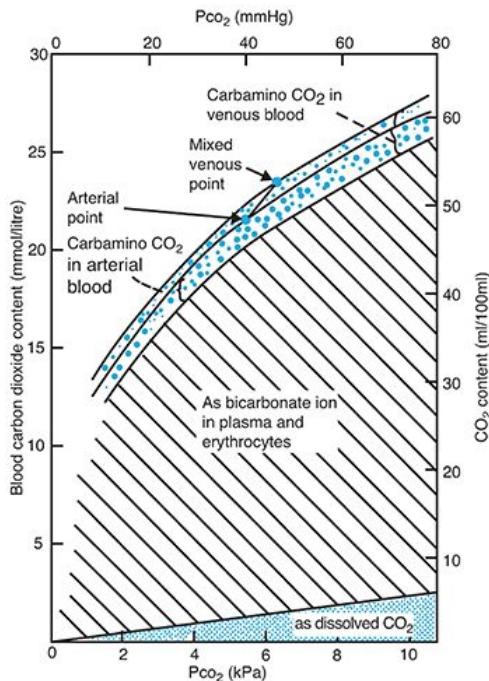


FIGURE 24.39 Transport of carbon dioxide (CO_2) in blood compared to the measured CO_2 tension. The tension dissolved CO_2 at the bottom is measured in blood gas analysis, but it is only the tip of the upside-down iceberg. The majority of CO_2 is transported as dissolved bicarbonate in the plasma and red blood cells. These vary with PCO_2 but are little affected by the oxygenation of hemoglobin. Carbamino transport of CO_2 is strongly influenced by the oxygenation of hemoglobin (the Haldane effect). *Reprinted from Lumb AB. Nunn's Applied Respiratory Physiology. 7th ed. Edinburgh: Churchill Livingstone/Elsevier; 2010. Copyright © 2010 Elsevier. With permission.*

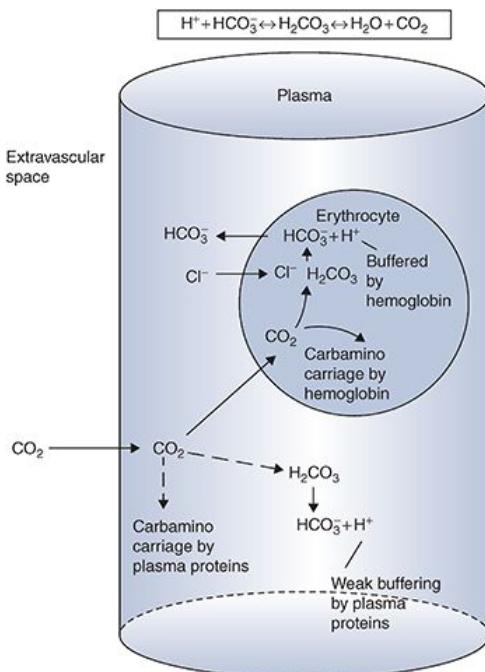


FIGURE 24.40 Carbon dioxide (CO_2) enters the plasma in molecular form from the tissues. The majority of CO_2 is transformed into bicarbonate (HCO_3^-) in the red blood cells; this reaction is catalyzed by carbonic anhydrase. A small proportion of plasma CO_2 is attached to plasma proteins as carbamino compounds or directly converted to HCO_3^- in the plasma. Some CO_2 in the red cell is also attached to hemoglobin as carbamino compounds. The excess hydrogen ions (H^+) generated in the red blood cell are transferred to the plasma in exchange for chloride ion (Cl^-). This is called the “chloride shift.” Abbreviations: H_2CO_3 , carbonic acid; H_2O , water. *Reprinted from Lumb AB. Nunn's Applied Respiratory Physiology. 7th ed. Edinburgh: Churchill Livingstone/Elsevier; 2010. Copyright © 2010 Elsevier. With permission.*

There are two effects that are involved in the physiology of gas transport in the blood. They can be remembered as follows:

1. Shifts of the OHb curve due to changes in H^+ , the Bohr effect ($b\text{OHr}$)
2. Changes in CO_2 transport due to changes in oxygen saturation, the Haldane effect (the other one)

Because the volume of CO_2 in blood is large compared to the volume of oxygen, for changes of approximately equal volumes of gas in the blood, the PCO_2 will change much less than the PO_2 . For example, the volume production of CO_2 is approximately 80% of the oxygen consumption. However, the difference in PCO_2 between venous and arterial blood is normally only 5 mm Hg, whereas the difference between arterial and venous PO_2 is typically 60 mm Hg.

Control of Respiration

Central Nervous System

The stimulus for normal breathing is generated spontaneously by a combination of at least six groups of neurons in the medulla of the brainstem. Each neuronal group seems to be primarily responsible for one phase of the respiratory cycle: early inspiration, late inspiration, early expiration, etc. The function of these neuronal groups is primarily under the control of the central chemoreceptor area, also in the medulla. The central chemoreceptor increases or decreases minute ventilation according to the cerebral spinal fluid pH to maintain normocapnia ([Figure 24.41](#)).⁴²

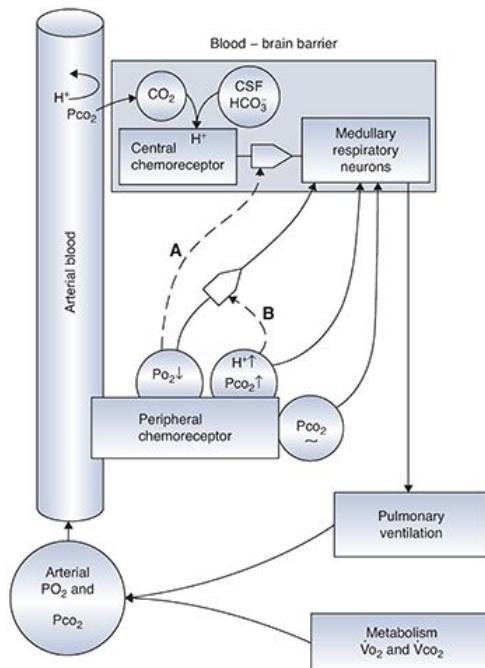


FIGURE 24.41 A diagram of the connections between individual components of the chemical and neural portions of the physiologic control of respiration (see text for details). Abbreviations: CO₂, carbon dioxide; CSF, cerebrospinal fluid; H⁺, hydrogen ion; HCO₃⁻, bicarbonate. *Reprinted from Lumb AB. Nunn's Applied Respiratory Physiology. 7th ed. Edinburgh: Churchill Livingstone/Elsevier; 2010. Copyright © 2010 Elsevier. With permission.*

Dissolved CO₂ in plasma diffuses easily across the blood–brain barrier into the cerebrospinal fluid (CSF) where it interacts with H₂O to form H⁺ and HCO₃⁻. The H⁺ concentration in the CSF is the primary controller for normal minute ventilation. The H⁺ and HCO₃⁻ in plasma cross the blood–brain barrier very slowly. The brainstem central chemoreceptor is acutely sensitive to changes in pH. Normally, an awake individual's Paco₂ will vary less than 3 mm Hg. If the PaO₂ is normal, minute ventilation will increase 2 to 3 L/minute for each 1 mm Hg increase in Paco₂ to restore arterial and CSF pH to normal levels. Ventilation will increase in a linear fashion as Paco₂ rises until a maximal stimulation somewhere over a Paco₂ of 100 mm Hg is reached or until the respiratory mechanics will no longer permit an increase in minute ventilation. At levels over 100 mm Hg, dissolved CO₂ in the CSF begins to exert a narcotic effect on the CNS.

The central chemoreceptor is acutely sensitive to CNS depressants. Opioids, sedatives, and most general anesthetics decrease the respiratory response to hypercapnia.

Peripheral Chemoreceptors

The peripheral chemoreceptors are located primarily in the carotid bodies at the bifurcation of the carotid arteries and also in aortic bodies above and below the aortic arch. These receptors respond primarily to changes in PaO₂.⁴³ They function as a backup system and in the normal individual do not have a primary role in control of ventilation. The innervation of the carotid bodies is via the glossopharyngeal nerve (CN IX) and the aortic bodies via the vagus nerve (CN X). Although there is some tonic activity from these peripheral chemoreceptors, they do not normally stimulate ventilation until the PaO₂ falls to below a threshold of approximately 70 to 80 mm Hg. This threshold will be lowered in individuals who are adapted to altitude and in some chronic respiratory or congenital hypoxic cardiac diseases. The nerve stimulus from the peripheral chemoreceptors has two complementary actions to increase ventilation. Primarily, there is a direct effect on the medullary respiratory neurons. Secondarily, there is an effect to increase the sensitivity to the stimulus of

the central chemoreceptor to CSF pH (dashed line A in [Figure 24.41](#)). The peripheral chemoreceptors also are sensitive to changes in arterial pH and PaCO_2 , and acidosis will increase the hypoxic drive (dashed line B in [Figure 24.41](#)). The hypoxic drive due to the peripheral chemoreceptors is decreased by volatile anesthetics, even in very low concentrations such as 0.1 minimum alveolar concentration, which are often present immediately after recovery from general anesthesia.⁴⁴ Although the hypercapnic response is also blunted in a dose-dependent fashion by volatile anesthetics, the response to hypoxemia is even more profoundly blocked.

Because of the combined effects of residual opioids on the central chemoreceptors and the blunting of hypoxic drive by trace amounts of volatile anesthetics, it is a common practice to initially administer supplemental oxygen to patients in the recovery room after general anesthesia then to follow the oxygen saturation using pulse oximetry as the supplemental oxygen is decreased prior to discharge. In the absence of shunt, with supplemental oxygen to raise the FiO_2 to 0.4, a patient's minute ventilation can fall temporarily to one-third of its normal value without significant hypoxemia (however, the PaCO_2 will rise and the pH will fall).

Other Neural Connections to the Medullary Respiratory Centers

The entire airway from the mucosal lining of the nose and mouth to the distal bronchi has both afferent and efferent neural connections to the central respiratory neurons. These connections are responsible for many of the normal respiratory reflexes such as the phasic inspiratory dilation of the upper airway during inspiration to maintain patency of the supraglottic airway. This reflex activity is easily reduced or eliminated by CNS sedatives and anesthetics and is responsible for much of the upper airway obstruction seen during anesthesia and compounds the airway obstruction in patients with obstructive sleep apnea (OSA). Irritants in the airway trigger cough and sneeze reflexes via these neuronal connections.

The lung has stretch receptors that, in the nonsedated state, respond to regional changes in compliance associated with atelectasis by triggering a recruitment maneuver such as a sigh or a yawn (if you are yawning as you read this, hopefully it is to recruit your lungs and not because the content is boring). Passive stretching of the lungs can result in either inhibition of inspiration (Herring-Breuer reflex) or gasping (Heads reflex) depending on the clinical context.

The pulmonary capillaries are densely innervated by unmyelinated nerves (C fibers). This innervation is not important during normal ventilation but may be responsible for causing a sensation of dyspnea when the capillaries become engorged during congestive heart failure.

Abnormal Breathing Patterns

Abnormal patterns of breathing are rare. There are several recognized abnormal patterns, which involve dysfunction of the central chemoreceptors. Primary alveolar hypoventilation syndrome (Ondine's curse) is a congenital insensitivity of the central chemoreceptor to changes in CSF pH. It results in apnea and hypoventilation, particularly during sleep. It can be treated with noninvasive ventilation and diaphragmatic pacing. Cheyne-Stokes respiration is a pattern of 10- to 20-second periods of apnea followed by periods of hyperventilation.⁴⁵ It is seen in some patients with CNS damage or severe illness and also during adaptation to altitude. It is caused by a delayed response interval in the central chemoreceptor. Cheyne-Stokes respiration is the most severe form of periodic breathing, which is seen to some degree in neonates and the elderly and during sleep at all ages.

Altered Physiologic Conditions

Anesthesia

Nunn⁴⁶ showed that during anesthesia and spontaneous ventilation, gas exchange was altered by shunt and inhomogeneous V/Q ratios. He concluded from his observations that a normal range of PaO_2 could be maintained if the PAO_2 was at least 200 mm Hg, which would require an FiO_2 of at least 35%. Brismar and colleagues⁴⁷ in 1985 demonstrated using computed tomography that within 5 minutes of the induction of

anesthesia, dependent regions of the lung developed an increase in density consistent with atelectasis. It is now accepted that this occurs in dependent lung regions in approximately 90% of patients who undergo general anesthesia using a wide variety of agents. Epidural anesthesia may be the one modality that appears to cause very little atelectasis and no change in VA/Q matching or oxygenation.

The near-universal finding of rapid lung collapse upon induction of anesthesia and the rapid reappearance after discontinuation of PEEP has led to the conclusion that atelectasis is due to compression of lung tissue rather than alveolar gas absorption behind occluded airways.⁴⁸ The fluoroscopic study by Froese and Bryan⁴⁹ of diaphragmatic motion of spontaneously breathing volunteers demonstrated that in the supine position, the dependent portion of the diaphragm has the greatest displacement with each breath. Initiation of paralysis with neuromuscular-blocking agents and positive pressure ventilation creates a reversal of this motion with the nondependent or superior aspect of the diaphragm undergoing the greatest displacement with each ventilated breath.⁴⁹ Others have confirmed and extended these observations using computed tomography.⁵⁰ It is now apparent that the geometry of the chest and diaphragm is altered under general anesthesia with relaxation of the chest wall and a marked cephalad displacement of the most dorsal portion of the diaphragm at end expiration.

Absorption atelectasis can occur when the rate of gas uptake into the blood exceeds the rate of ventilation of the alveolus. The extreme condition is total occlusion of an airway, which isolates the alveolar gas in the distal alveolar and respiratory airways. The gas pressure within this compartment initially is nearly at atmospheric pressure. However, given that mixed venous blood continues to perfuse this area, and the fact that the sum of the gas partial pressures within mixed venous blood is subatmospheric, gas uptake from the occluded compartment by blood continues and the alveoli collapses. Computer modeling has demonstrated that the rate of gas absorption from unventilated areas is dependent on the initial FIO_2 .⁵¹ Higher initial FIO_2 (100% vs 30%) has been shown to produce clear atelectasis immediately following induction of anesthesia, which increases by 40 minutes following induction. This is also associated with a measurable increase in shunting.⁵² However, in many clinical situations, the airway is not completely occluded but rather ventilation to an area becomes severely reduced. If the inspired VA/Q ratio of a respiratory unit is reduced, a point is reached where the rate at which inspired gas enters the alveolus is exactly balanced by the gas uptake into the blood. If VA/Q ratio drops below this critical equilibrium point, the volume of the alveolus declines and collapse ensues. Again, this process is augmented by the presence of a high PAO_2 and a rapid rate of gas uptake.

Loss of alveolar surfactant may play a role in alveolar instability at low alveolar volumes and collapse. The rapidity of alveolar collapse following alveolar recruitment maneuvers and discontinuation of PEEP has suggested that atelectasis per se may interfere with surfactant production. Therefore, atelectatic regions of the lung may be predisposed to recurrence of collapse because of reduced levels of surfactant, increased alveolar surface tension, and, the aforementioned mechanisms, all contributing to reduced alveolar volumes. The effects of anesthetic drugs on HPV and V/Q matching are considered in [Chapter 25](#).

Position

In the spontaneously breathing patient, awake or during anesthesia, the majority of gas exchange are due to caudal displacement of the diaphragm, which occurs primarily in the dorsal portions of the thoraces. During deep anesthesia and paralysis, the diaphragm becomes relatively flaccid. The weight of the abdominal contents pushes cranially on the dorsal diaphragm, and during inspiration, with positive pressure ventilation, gas preferentially distributes to the now more compliant ventral portions of the lungs.⁵³ The distribution of perfusion remains largely unchanged with predominance to the central and dependent portions of the lung. Thus, matching of V/Q is decreased with induction of anesthesia and further decreased with paralysis and positive pressure ventilation. The addition of low levels of PEEP (<10 cm H₂O, after recruitment) will usually ameliorate this mismatch by slightly overdistending ventral lung regions but moving dependent lung regions to a more compliant portion of their pressure-volume curve.

During anesthesia and positive pressure ventilation in the prone position, the majority of diaphragm displacement during inspiration will remain in the dorsal (now the nondependent) portions of the thoraces and

ventilation will be more homogeneously distributed in the lungs compared to the supine position. Matching of ventilation to perfusion will usually be superior in the prone position when compared with the supine position. However, unlike the supine position, the addition of PEEP in the prone position may lead to deterioration in V/Q matching.⁵⁴ This applies to patients with normal lungs. This is unlike the situation in the patient with ARDS. In these patients in the supine position, pulmonary edema collects in the parenchyma of the dorsal portions of the lung. The combination of prone position and PEEP may lead to a more favorable matching of ventilation to perfusion. Prone positioning in ARDS has been shown to improve lung elastance, transpulmonary driving pressure, $\text{PaO}_2/\text{FiO}_2$, and Paco_2 clearance in the early period after placing a patient prone.⁵⁵ However, this effect may not be persistent.

The effects of the lateral position are discussed in the “One-Lung Ventilation” section.

Obesity

The increased weight of the abdominal contents and chest wall impose a restrictive ventilatory pattern on the respiratory system with a decrease of all lung volumes but a preservation of the FEV_1/FVC ratio.⁵⁶ This is primarily important to the anesthesiologist because of the fall in FRC, which leads to increased venoarterial shunt and a tendency to desaturate during induction and maintenance of anesthesia and in the postoperative period. The FRC of an awake mildly obese patient of body mass index (BMI) 30 kg/m^2 will be 75% of predicted for a similar person, but with a BMI of 20 kg/m^2 and for a patient with a BMI $>40 \text{ kg/m}^2$, the FRC will be <66% predicted. Elevated BMI has been shown to be associated with reduced resting PaO_2 and larger A-a gradient, which are thought to be the consequence of reduced expiratory reserve volume.⁵⁷

Early studies of PEEP during anesthesia in obese patients showed mixed results in terms of improving oxygenation. This is due to the rapid development of atelectasis in these patients and the inability of PEEP, by itself, to correct atelectasis. As can be seen in **Figure 24.42**, the combination of a recruitment maneuver and $10 \text{ cm H}_2\text{O}$ PEEP can eliminate atelectasis in a morbidly obese patient. The challenge in respiratory management of the obese patient perioperatively is to minimize the fall in FRC. This can be done with a variety of methods including the use of regional anesthesia/analgesia, avoiding long-acting muscle relaxants, positioning, and the use of postoperative CPAP.

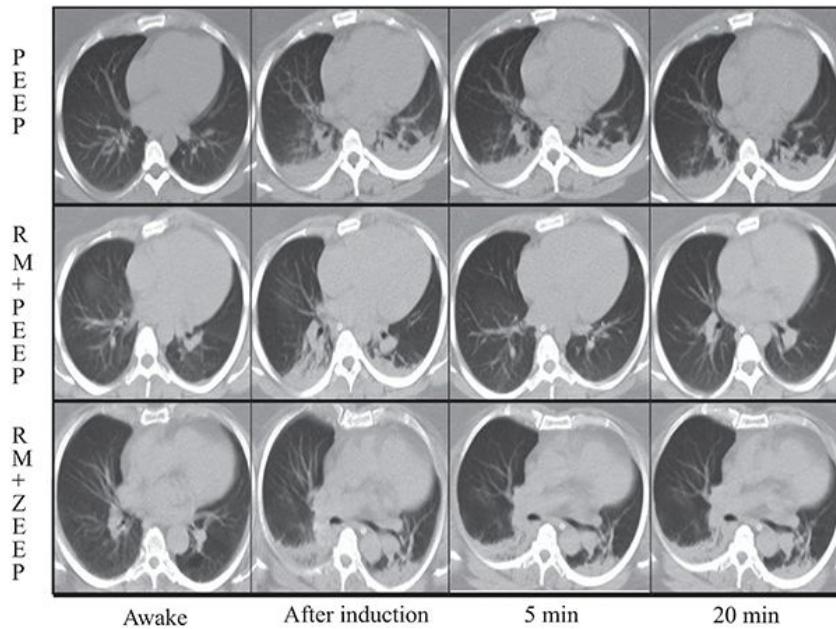


FIGURE 24.42 Each row is a representative computerized tomography scan 1 cm above the diaphragm in three different morbidly obese patients during anesthesia. The patient on the top row received $10 \text{ cm H}_2\text{O}$ positive end-expiratory pressure (PEEP). The patient in the middle row received a recruitment maneuver

(RM) ($55 \text{ cm H}_2\text{O} \times 10 \text{ seconds}$) after induction plus PEEP $10 \text{ cm H}_2\text{O}$. The patient in the bottom row received an RM and then a zero end-expiratory pressure (ZEEP).

Sleep-Disordered Breathing

Approximately 20% of the population has disorders of respiration during sleep ranging from simple snoring to OSA. These disorders all involve variable degrees of upper airway obstruction and apnea during normal sleep. The OSA is defined as more than five episodes per hour of apnea, each >10 seconds. It is often combined with periods of hypopnea in the sleep apnea hypopnea syndrome (SAHS). The OSA may be exacerbated by fluid shifts to the upper body from the legs during sleep in patients with sedentary lifestyles.⁵⁸ The disturbance of normal sleep leads to daytime somnolence, and the periods of hypoxia may contribute to cardiovascular morbidity. Treatments may include weight loss, CPAP devices, and upper airway surgery.⁵⁹ The obesity hypoventilation syndrome is a combination of obesity, hypoventilation, and severe OSA, which has been called the **Pickwickian** syndrome.⁶⁰

Exercise

Normal oxygen consumption at rest is approximately 200 to 250 mL/minute (3-4 mL/kg/minute) for an adult; this is termed **1 metabolic equivalent** (MET). Quick walking or climbing one flight of stairs requires 4 METs, bowling 8 METs, and competitive cross-country skiing 14 METs. Olympic rowers, skiers, and cyclists may exceed 80 mL/kg/minute oxygen consumption (20 METs).⁶¹ To achieve this increase in oxygen consumption requires matching increases in minute ventilation and cardiac output. At a certain point, the increases in ventilation and cardiac output will not be able to supply adequate oxygen to the tissues for aerobic metabolism and further increase in muscle activity will require anaerobic metabolism producing lactic acid. This is called the **anaerobic threshold**. It is most often the accumulation of lactate in tissues causing muscle dysfunction, which limits prolonged exercise and not a limitation on minute ventilation or cardiac output. Exercise training raises the maximal oxygen consumption ($\text{VO}_{2\text{max}}$), the anaerobic threshold, and the tolerance for lactic acidosis. Cardiopulmonary exercise testing (CPET) is an established medical procedure to measure a patient's $\text{VO}_{2\text{max}}$ or to distinguish between respiratory and cardiac limitations in exercise capacity. The $\text{VO}_{2\text{max}}$ has been shown to be a useful preoperative test to identify patients at increased risk for complications from pulmonary resection surgery (preoperative $\text{VO}_{2\text{max}} < 15-20 \text{ mL/kg/minute}$).¹⁵

Although the predictive utility of CPET in other surgeries has previously been unclear, emerging evidence has shown promise. A recent meta-analysis has shown CPET to be useful in predicting 90-day survival as well as overall morbidity and mortality in hepatic resection, hepatic transplant, pancreatic, and general intra-abdominal surgery.⁶² Similarly, CPET poor performance is associated with higher cardiopulmonary complications following open abdominal aorta repair.⁶³

A useful estimate of a COPD patient's $\text{VO}_{2\text{max}}$ can be made from the maximal distance they can walk in 6 minutes the "6-minute walk test" (6MWT). If the distance in meters is divided by 30, the result is an approximation of the $\text{VO}_{2\text{max}}$ (eg, 6MWT distance = 450 m, $\text{VO}_{2\text{max}} = 450 / 30 = 15 \text{ mL/kg/minute}$).⁶⁴

Altered Barometric Pressures

The ambient PO_2 decreases proportionally as the barometric pressure falls with increases in altitude. The PO_2 is 149 mm Hg at sea level, 122 at 5,000 ft of elevation (eg, Denver), and may be as low as 108 mm Hg in a commercial airliner pressurized to 8,000 ft (maximum permitted altitude equivalent). For comparison, on the summit of Mount Everest, the PO_2 is 47 mm Hg (63,000 ft). There are both acute and chronic adaptations to the hypoxia associated with altitude. Primarily, the rapid adaptation involves hyperventilation, driven by the peripheral chemoreceptors to decrease the alveolar PCO_2 and thus increase the alveolar PAO_2 . The secondary alkalinization of blood and CSF returns to normal after several days at altitude as HCO_3^- is excreted. The increased pulmonary pressures due to HPV triggered by hypoxia can lead to high-altitude pulmonary edema. This can be treated with oxygen, diuretics, and pulmonary vasodilators. Increased cerebral blood flow due to

hypoxia is opposed in part by the cerebral vasoconstriction due to hypocapnia but may lead to cerebral edema. Chronic acclimatization to altitude involves a variety of cellular and metabolic changes such as a resetting of the peripheral chemoreceptors and polycythemia.

Anesthesia at mild elevations is generally uncomplicated as long as oxygen saturation is monitored and adequate supplemental oxygen is provided. This can be a problem with nitrous oxide. Most modern commercial vaporizers deliver reasonably accurate dosages of volatile anesthetics at modest elevations (<6,000 ft). Pressure in the air-filled cuff of an endotracheal tube or laryngeal mask airway will increase and decrease significantly with changes in ambient pressure, which may be associated with medical air transport.⁶⁵

Hyperbaric oxygen in medical practice is delivered in a chamber pressurized to 2 to 3 times atmospheric pressure (atm) (ie, 1,400-2,100 mm Hg). Treatments are given with a high FIO_2 , usually from a tight-fitting mask for several hours and repeated as required.⁶⁶ Indications include gas embolism, decompression sickness, necrotizing soft tissue infections, and carbon monoxide poisoning. At high FIO_2 levels, above 2 atm, hyperoxia may cause convulsions. Prolonged exposure to a high PAO_2 causes pulmonary oxygen toxicity and a restrictive lung disease. A high PAO_2 in the neonate can cause retrolental fibroplasia, ultimately damaging the retina of the eye.

Age

Infants and Children

The overall C_{RS} is low in newborns and increases until late adolescence. Alveoli at birth have a lower amount of elastin than adults and a decreased amount of surfactant leading to decreased lung compliance. However, the C_{cw} in newborns and infants is very high due to the absence of ossification of cartilages. This predisposes infants to a significant fall in FRC during anesthesia. In the awake state, FRC is maintained above CC in infants by a rapid respiratory rate. The respiratory muscles of infants have a lower percentage of fatigue-resistant type I fibers, and they are more prone to respiratory fatigue. All airways are proportionately smaller in infants than adults, and airway resistance is higher, resulting in increased work of breathing at rest and particularly during upper or lower airway infections (eg, croup). The narrowest portion of the upper airway is at the cricoid cartilage until age 5 years.⁶⁷

Control of breathing in the newborn is unique. Hypoxia initially causes increased ventilation, as in the adult, but then leads to a decrease in ventilation.⁶⁸ This is more exaggerated in preterm infants. Oxygen consumption is higher in newborns than in adults (6-8 mL/kg/minute). The HbF predominates at birth until 3 to 6 months of age. The HbF has a low P_{50} (18-19 mm Hg), which increases oxygen loading in the placenta but decreases oxygen unloading in the tissues.

The Elderly

Changes in the respiratory system with age include decrease of muscle tone in the dilators of the pharynx, predisposing to upper airway obstruction during anesthesia.⁶⁹ There is a loss of the pulmonary vascular bed, which results in an increase of PVR and a 30% increase in mean P_{PAs} and an increase in the alveolar dead space. The lung parenchyma loses elastic support tissue, resulting in an increase of lung compliance, but the chest wall increases in stiffness, so the net effect is an overall decrease in respiratory system compliance. With the loss of structural support of peripheral airways, the CC increases significantly; this is the change, which has major anesthetic implications. The fall of FRC below CC leads to increased venoarterial shunt and is responsible for the decrease in PaO_2 with age. The mean PaO_2 of healthy patients will decline to approximately 80 mm Hg at age 70, after which it remains stable. The responsiveness of both central and peripheral chemoreceptors to hypercarbia and hypoxemia decreases with age.

Chronic Respiratory Disease

Chronic respiratory disease is commonly divided into two major categories: obstructive and restrictive. In obstructive disease, the FEV_1/FVC ratio is typically less than normal (<80%) with a decreased FEV_1 .

Restrictive disease typically has a normal FEV₁/FVC ratio and a decreased FEV₁. There is some overlap, with some patients (eg, cystic fibrosis) showing a mixed obstructive/restrictive pattern. Severity of these diseases can be graded according to the FEV₁ as a percentage of predicted values: mild, FEV₁ >70%; moderate, 50% to 70%; severe, 30% to 50%; and very severe, <30%.

The COPD incorporates three disorders: emphysema, peripheral airways disease, and chronic bronchitis. Any individual patient may have one or all of these conditions, but the dominant clinical feature is impairment of expiratory airflow. Life expectancy may be less than 3 years in severe COPD patients >60 years of age. Mild COPD patients should not have significant dyspnea, hypoxemia, or hypercarbia, and other causes should be considered if these are present.⁷⁰

Some moderate and severe COPD patients have an elevated PacO₂ at rest. It is not possible to differentiate these “CO₂ retainers” from nonretainers on the basis of history, physical examination, or spirometric pulmonary function testing. This CO₂ retention seems to be related to an inability to maintain the increased work of respiration required to keep the PacO₂ normal in patients with mechanically inefficient pulmonary function and not primarily due to an alteration of respiratory control mechanisms. The PacO₂ rises in these patients when supplemental FIO₂ is administered due to a relative decrease in VA and an increase in alveolar dead space and shunt by the redistribution of perfusion away from lung areas of relatively normal V/Q matching to areas of very low V/Q ratio because regional HPV is decreased and also due to the Haldane effect.⁷¹ However, supplemental oxygen must be administered to these patients postoperatively to prevent the hypoxemia associated with the unavoidable fall in FRC. The attendant rise in PacO₂ should be anticipated and monitored. To identify these patients preoperatively, all moderate or severe COPD patients need an arterial blood gas analysis. Also, it is important to know the patient’s baseline preoperative PacO₂ to guide weaning if mechanical ventilation becomes necessary in the postoperative period.

The COPD patients desaturate more frequently and severely than normal patients during sleep.⁷² This is due to the rapid/shallow breathing pattern that occurs in all patients during REM sleep. In COPD patients breathing air, this causes a significant increase in the VD/VT and a fall in alveolar oxygen tension (PAO₂) and PaO₂. This is not the SAHS. There is no increased incidence of SAHS in COPD.

Right ventricular dysfunction occurs in up to 50% of moderate to severe COPD patients.⁷³ The dysfunctional right ventricle is poorly tolerant to sudden increases in afterload such as the change from spontaneous to controlled ventilation. Right ventricular function becomes critical in maintaining cardiac output as the P_{PA} rises. The right ventricular ejection fraction does not increase with exercise in COPD patients as it does in normal patients. Chronic recurrent hypoxemia is the cause of the right ventricular dysfunction and the subsequent progression to cor pulmonale. Patients who have episodic hypoxemia in spite of normal lungs (eg, central alveolar hypoventilation, SAHS) develop the same secondary cardiac problems as COPD patients. The only therapy that has been shown to improve long-term survival and decrease right heart strain in COPD is supplemental oxygen. The COPD patients who have resting PaO₂ less than 55 mm Hg should receive supplemental home oxygen and also those who desaturate to less than 44 mm Hg with exercise. The goal of supplemental oxygen is to maintain a PaO₂ 60 to 65 mm Hg. Compared to patients with chronic bronchitis, emphysematous COPD patients tend to have a decreased cardiac output and mixed venous oxygen tension while maintaining lower P_{PA}s.

Many patients with moderate or severe COPD will develop cystic air spaces in the lung parenchyma known as **bullae** ([Figure 24.43](#)). These bullae will often be asymptomatic unless they occupy more than 50% of the hemithorax, in which case the patient will present with findings of restrictive respiratory disease in addition to their obstructive disease. A bulla is a localized area of loss of structural support tissue in the lung with elastic recoil of surrounding parenchyma ([Figure 24.44](#)).⁷⁴ The pressure in a bulla is actually the mean pressure in the surrounding alveoli averaged over the respiratory cycle. This means that during normal spontaneous ventilation, the intrabulla pressure is actually slightly negative in comparison to the surrounding parenchyma. However, whenever positive pressure ventilation is used, the pressure in a bulla will become positive in relation to the adjacent lung tissue and the bulla will expand with the attendant risk of rupture,

tension pneumothorax, and bronchopleural fistula. Positive pressure ventilation can be used safely in patients with bullae provided the airway pressures are kept low and there is adequate expertise and equipment immediately available to insert a chest drain and obtain lung isolation if necessary. Due to the lower solubility of nitrogen in plasma compared to nitrous oxide, when a patient is converted from breathing air to breathing a mixture containing nitrous oxide during anesthesia, the nitrous oxide will diffuse into a bulla faster than the nitrogen can be absorbed and the bulla will increase in size with the attendant risk of rupture.



FIGURE 24.43 Coronal computed tomography scan of a patient with bilateral giant lower lobe bullae. During positive pressure ventilation, the risk of bulla rupture and tension pneumothorax must always be kept in mind.



FIGURE 24.44 A, A spider's web seen on a woodbox on a sunny day as a lung model to demonstrate the pathophysiology of bullae. B, Breaking one septum of the spider's web causes a bulla to appear as elastic recoil pulls the web away from the area where structural support has been lost. Although the cells surrounding the bulla appear compressed, this is only due to redistribution of elastic forces. It is not positive pressure inside the bulla that causes this appearance of surrounding compression.

Severe COPD patients are often “flow limited” even during tidal volume expiration at rest. Flow limitation is present in normal patients only during a forced expiratory maneuver. Flow limitation occurs when an EPP develops in the intrathoracic airways during expiration. During quiet expiration in the normal patient, the pressure in the lumen of the airways always exceeds the intrapleural pressure because of the upstream elastic recoil pressure, which is transmitted from the alveoli. The effect of this elastic recoil pressure diminishes as air flows downstream in the airway. With a forced expiration, the intrapleural pressure may equal the intraluminal pressure at a certain point, the EPP, which then limits the expiratory flow (see [Figure 24.27](#)). Then, any increase in expiratory effort will not produce an increase in flow at that given lung volume. Flow limitation occurs particularly in emphysematous patients, who primarily have a problem with loss of lung elastic recoil and have marked dyspnea on exertion. Flow limitation causes dyspnea because of stimulation of mechanoreceptors in the muscles of respiration, thoracic cage, and in the airway distal to the EPP. Any increase in the work of respiration will lead to increased dyspnea. This variable mechanical

compression of airways by overinflated alveoli is the primary cause of the airflow obstruction in emphysema. Severely flow-limited patients are at risk for hemodynamic collapse with the application of positive pressure ventilation due to dynamic hyperinflation of the lungs. Even the modest positive airway pressures associated with manual ventilation with a bag/mask at induction can lead to hypotension because these patients have no increased resistance to inspiration but a marked obstruction of expiration. In some of these patients, this has contributed to the “Lazarus” syndrome in which patients have recovered from a cardiac arrest only after resuscitation and positive pressure ventilation were discontinued.⁷⁵

Patients with severe COPD often breathe in a pattern that interrupts expiration before the alveolar pressure has fallen to atmospheric pressure. This incomplete expiration is due to a combination of factors, which include flow limitation, increased work of respiration, and increased airway resistance. This interruption leads to an elevation of the end-expiratory lung volume above the FRC. This PEEP in the alveoli at rest has been termed **auto-PEEP** or **intrinsic PEEP**. During spontaneous respiration, the intrapleural pressure will have to be decreased to a level, which counteracts auto-PEEP before inspiratory flow can begin. Thus, COPD patients can have an increased inspiratory load added to their already increased expiratory load.

Auto-PEEP becomes even more important during mechanical ventilation. It is directly proportional to tidal volume and inversely proportional to expiratory time. The presence of auto-PEEP is not detected by the manometer of standard anesthesia ventilators. It can be measured by end-expiratory flow interruption, a feature available on most intensive care ventilators. Auto-PEEP has been found to develop in most COPD patients during one-lung anesthesia.⁷⁶

Restrictive lung diseases are often part of a multisystemic disease process such as connective tissue disorders. In a minority of patients, there is no other systemic disease (ie, idiopathic pulmonary fibrosis). Patients are often more debilitated by their underlying disease (eg, rheumatoid arthritis) than their lung disease. Patients with mild to moderate restrictive lung disease are, in general, less of a problem for the anesthesiologist to manage intraoperatively (compared to COPD) and more of a problem postoperatively. Due to the decrease in FRC in restrictive disease, these patients tend to develop an increased shunt during anesthesia and postoperatively. Restoration of the FRC postoperatively is commonly a problem, and the use of regional anesthesia/analgesia, short-acting opioids and muscle relaxants, and noninvasive ventilation are often of benefit in the patient with restrictive disease.

One-Lung Ventilation

An OLV is performed during thoracic surgery to facilitate the surgical exposure in the chest. The OLV is commonly obtained by placement of a double-lumen endobronchial tube or a bronchial blocker with a standard endotracheal tube. During OLV, the anesthesiologist has the unique and often conflicting goals of trying to maximize atelectasis in the nonventilated lung to improve surgical access while trying to avoid atelectasis in the ventilated lung (usually the dependent lung) to optimize gas exchange. The gas mixture in the nonventilated lung immediately before OLV has a significant effect on the speed of collapse of this lung.⁷⁷ Because of its low blood gas solubility, nitrogen (or an air-oxygen mixture) will delay collapse of this lung. This is particularly a problem at the start of minimally invasive thoracic surgery when surgical visualization in the operative hemithorax is limited and in patients with emphysema who have delayed collapse of the nonventilated lung due to decreased lung elastic recoil. It is important to thoroughly denitrogenate the operative lung, by ventilating with oxygen, immediately before it is allowed to collapse. Although nitrous oxide is even more effective than oxygen in speeding lung collapse (because of its solubility), it is not commonly used in thoracic anesthesia because many patients may have blebs or bullae. During the period of two-lung anesthesia before the start of OLV, atelectasis will develop in the dependent lung. It is useful to perform a recruitment maneuver to the dependent lung (similar to a Valsalva maneuver, holding the lung at an end-inspiratory pressure of 20 cm H₂O for 15-20 seconds) immediately after the start of OLV to decrease this atelectasis. Recruitment is important to maintain Pao₂ levels during subsequent OLV.⁷⁸

A major concern that influences anesthetic management for thoracic surgery is the occurrence of hypoxemia during OLV. There is no universally acceptable figure for the safest lower limit of oxygen

saturation during OLV. A saturation greater than or equal to 90% ($\text{PaO}_2 > 60 \text{ mm Hg}$) is commonly accepted, and for brief periods, a saturation in the high 80s may be acceptable in patients without significant comorbidity. However, the lowest acceptable saturation will be higher in patients with organs at risk for hypoxia due to limited regional blood flow (eg, coronary or cerebrovascular disease) and in patients with limited oxygen transport (eg, anemia or decreased cardiopulmonary reserve). Previously, hypoxemia occurred frequently during OLV. Reports for the period 1950-1980 describe an incidence of hypoxemia (arterial saturation $< 90\%$) of 20% to 25%. Current reports describe an incidence of less than 5%. This improvement is most likely due to several factors: improved lung isolation techniques, such as routine fiberoptic bronchoscopy to prevent lobar obstruction from double-lumen tubes; improved anesthetic agents, which cause less inhibition of HPV; and better understanding of the pathophysiology of OLV.

The pathophysiology of OLV is complex and involves the body's ability to redistribute pulmonary blood flow to the ventilated lung. Several factors aid and impede this redistribution, and these are under the control of the anesthesiologist to a variable degree. These factors are illustrated in [Figure 24.45](#). The anesthesiologist's goal during OLV is to maximize PVR in the nonventilated lung while minimizing PVR in the ventilated lung. The PVR is lowest at FRC and increases as lung volume rises or falls above or below FRC. The anesthesiologist's aim, to optimize pulmonary blood flow redistribution during OLV, is to maintain the ventilated lung as close as possible to its FRC while facilitating collapse of the nonventilated lung to increase its PVR.⁷⁹ Most thoracic surgery is performed in the lateral position. Patients having OLV in the lateral position have significantly better PaO_2 levels than patients during OLV in the supine position due to a preferential distribution of blood flow to the dependent lung caused by gravitational forces.

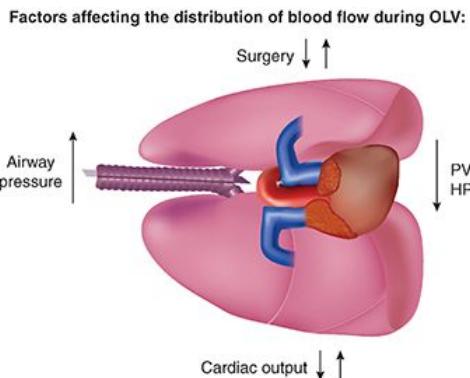


FIGURE 24.45 Factors affecting the distribution of pulmonary blood flow during one-lung ventilation (OLV). Hypoxic pulmonary vasoconstriction (HPV) and the collapse the nonventilated lung, which increase pulmonary vascular resistance (PVR), tend to distribute blood flow toward the ventilated lung. The airway pressure gradient between the ventilated and nonventilated thoraces tends to encourage blood flow to the nonventilated lung. Surgery and cardiac output can have variable effects either increasing or decreasing the proportional flow to the ventilated lung. Gravity will also increase the blood flow to the dependent lung.

Ventilatory strategies during OLV have shifted from historical practice focusing on higher tidal (10 mL/kg) volumes and FiO_2 with or without PEEP to more lung protective strategies based on intensive care literature. In this setting, the use of lower tidal volumes (6 mL/kg), routine use of PEEP recruitment maneuvers, and FiO_2 titrated to SpO_2 or PaO_2 have become more commonplace and recommended.⁸⁰ That being said, the role of lung protective strategies in reducing pulmonary complications during OLV remains inconsistent. More recently, lung protective ventilation strategies have moved beyond low tidal volume and routine use of PEEP to incorporate strategies to individualize ventilation based on compliance. Minimization of “driving pressure” (DP), which is calculated as $\text{DP} = \text{plateau pressure} - \text{PEEP}$, has been shown to reduce postoperative pulmonary complications. Minimization of DP is achieved through titration of both tidal volume and PEEP intraoperatively after performance of recruitment maneuvers. Recent observational and

randomized controlled trials in thoracic surgery patients have shown a reduction in postoperative pulmonary complications.[81,82](#)

Extracorporeal Ventilatory Support

Various devices to supplement or replace the gas exchange function of the lung have been available clinically for the past several decades. These devices have been associated with a high incidence of complications, particularly cerebral hemorrhage and infarction, and have met with questionable outcome results in several studies. However, gradual progress in the technology has seen a resurgence of use of these devices.[83](#) Indications currently may include infant respiratory distress syndrome, adult respiratory distress syndrome, respiratory failure unresponsive to mechanical ventilation, and as a bridge to transplantation in end-stage lung diseases. During extracorporeal ventilation, less injurious mechanical ventilation strategies can be used on the native lungs with relatively normal FIO_2 and tidal volumes to allow some regression of the disease process in the lungs.

The options for extracorporeal ventilatory support include venovenous membrane oxygenation, with an oxygenator and a pump, indicated in primary respiratory failure; venoarterial membrane oxygenation, for combined respiratory and cardiac failure; and pumpless interventional lung assist, with a passive arterial-venous membrane gas-exchange device, which is primarily used in failure of CO_2 excretion with relatively maintained oxygenation.[84](#)

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Respiratory Pharmacology

Peter Slinger

This chapter reviews the pharmacology of agents commonly encountered in anesthetic practice that are either administered to treat pulmonary diseases or administered into the airway or systemically for action at end organs other than the lung but have effects on the airway and the pulmonary circulation. The pharmacology of the airways is considered first, then the pharmacology of the pulmonary circulation, and finally, the intrinsic action of the lungs on a variety of exogenous and endogenous substances.

Pharmacology of the Airways

Pharmacologic agents administered via the lungs take advantage of the interface between air and blood allowing for rapid uptake of drugs into the bloodstream or immediate use by cells that populate the airway.¹ The delivery of medications to the lungs can have systemic effects, direct effects on the airway, or both. For example, inhaled anesthetics are delivered via the lungs to act in the brain and have bronchodilatory effects. Conversely, β -adrenergic agonists delivered via aerosol exert direct effects on bronchial smooth muscle with few systemic effects. Drugs administered to the airway take advantage of the rapid exposure to blood and pulmonary parenchymal cells, making them advantageous for treating pulmonary parenchymal diseases such as asthma and chronic obstructive pulmonary disease (COPD).

Influence of the Autonomic Nervous System on the Airways

Traditionally, the autonomic nervous system has been divided into two major parts, the parasympathetic and sympathetic nervous systems. The parasympathetic nervous system regulates airway caliber, airway glandular activity, and airway microvasculature.²⁻⁴ The vagus nerve provides the preganglionic fibers, which synapse with postganglionic fibers in airway parasympathetic ganglia. Acetylcholine activates the muscarinic 3 (M3) receptor of postganglionic fibers of the parasympathetic nervous system to produce bronchoconstriction.⁵ Anticholinergics can provide bronchodilation even in the resting state because the parasympathetic nervous system produces a basal level of resting bronchomotor tone.⁶

Although the sympathetic nervous system plays no direct role in control of airway muscle tone, β_2 -adrenergic receptors are present on airway smooth muscle cells and cause bronchodilation via stimulatory G mechanisms. The abundance of these receptors in the airway allows for pharmacologic manipulation of airway tone.⁷

The autonomic nervous system also influences bronchomotor tone through the nonadrenergic noncholinergic (NANC) system.^{8,9} The exact role of NANC in humans is not well defined; it has excitatory and inhibitory neuropeptides that influence inflammation and smooth muscle tone, respectively. Vasoactive intestinal peptide and nitric oxide (NO) are the main inhibitory transmitters thought to be responsible for airway smooth muscle relaxation. Substance P and neurokinin A are the main excitatory transmitters and have been shown to cause neurogenic inflammation, including bronchoconstriction. The precise role of NANC in healthy and diseased human lung is unclear.

Inhaled Adrenergic Agonists

The mainstay of therapy for bronchospasm, wheezing, and airflow obstruction is β -adrenergic agonists. β -Adrenergic agonists used in clinical practice are typically delivered via inhalers or nebulizers, are β_2 selective, and are divided into short- and long-acting therapies.¹⁰ Short-acting β_2 agonist therapy is effective for the rapid relief of wheezing, bronchospasm, and airflow obstruction. Longer acting β_2 agonists are used as

maintenance therapy providing improvement in lung function and reduction in symptoms and exacerbations ([Table 25.1](#)).

TABLE 25.1

Pharmacologic influence on the autonomic nervous system^a

Systemic adrenergic agonists	Inhaled adrenergic agonists	Inhaled cholinergic antagonists	Systemic cholinergic antagonists
	Short acting	Short acting	
Terbutaline	Albuterol	Ipratropium	Atropine
Epinephrine	Levalbuterol		Scopolamine
Albuterol	Metaproterenol		Glycopyrrolate
	Pirbuterol		
	Long acting	Long acting	
	Salmeterol	Tiotropium	
	Formoterol		
	Arformoterol		

^aReprinted by permission from Springer: Bailey C, Wojciechowski PJ, Hurford WE. Pharmacology of the airways. In: Slinger P, ed. *Principles and Practice of Anesthesia for Thoracic Surgery*. 2nd ed. Cham, Switzerland: Springer; 2019:151-164. Copyright © 2019 Springer Nature Switzerland AG.

Short-acting β_2 agonists bind to the β_2 -adrenergic receptor located on the plasma membrane of smooth muscle cells, epithelial, endothelial, and many other types of airway cells.¹¹ This causes a stimulatory G protein to activate adenylate cyclase converting adenosine triphosphate into cyclic adenosine monophosphate (cAMP). It is unknown precisely how cAMP causes smooth muscle relaxation; however, decreases in calcium release and alterations in membrane potential are the most likely mechanisms. Longer acting β_2 agonists have the same mechanism of action as short-acting β_2 agonists; however, they have unique properties that allow for a longer duration of action. For example, salmeterol has a longer duration of action because a side chain binds to the β_2 -receptor and prolongs the activation of the receptor.¹² The lipophilic side chain of formoterol allows for interaction with the lipid bilayer of the plasma membrane and a slow, steady release prolonging its duration of action.

β_2 Agonists have a central role in the management of obstructive airway diseases allowing for control of symptoms and improvement in lung function. Short-acting β_2 agonists such as albuterol, levalbuterol, metaproterenol, and pirbuterol are prescribed for the rapid relief of wheezing, bronchospasm, and airflow obstruction. Clinical effect is seen in a matter of minutes and lasts up to 4 to 6 hours. Scheduled, daily use of short-acting β_2 agonists has largely fallen out of favor, and they are now used primarily as rescue therapy.¹³⁻¹⁵ Long-acting β_2 agonists are prescribed for control of symptoms when rescue therapies (ie, short-acting β_2 agonists) are used greater than two times per week.¹⁶ Combination therapy including a long-acting β_2 agonist and an inhaled corticosteroid is effective in reducing symptoms, reducing the risk of exacerbation, and improving lung function while minimizing the dose of inhaled corticosteroid.¹⁷

Systemic absorption of inhaled β_2 agonists is responsible for a myriad of side effects, most of which are not serious. Most commonly, β_2 agonist therapy leads to tremors and tachycardia secondary to direct stimulation of the β_2 -adrenergic receptor in skeletal muscle or vasculature, respectively.^{18,19} In severe asthma, β_2 agonists may cause a temporary reduction in arterial oxygen tension of 5 mm Hg or more, secondary to β_2 -mediated vasodilation in poorly ventilated lung regions.²⁰ Hyperglycemia, hypokalemia, and hypomagnesemia also can occur with β_2 agonist therapy, but the severity of these side effects tends to diminish with regular use. Tolerance to β_2 agonists can occur with regular use over a period of weeks and, while not affecting peak bronchodilation, can be evidenced by a decrease in the duration of bronchodilation.

and the magnitude of side effects (tremor, tachycardia, etc).^{21,22} Tolerance likely reflects β_2 -adrenergic receptor downregulation. β_2 Agonist therapy withdrawal after regular use can produce transient bronchial hyperresponsiveness.

Evidence has associated the use of long-acting β_2 agonist therapy without concomitant use of a steroid inhaler with fatal and near-fatal asthma attacks.²³ In light of this evidence, it seems prudent to reserve long-acting β_2 agonists for patients who are poorly controlled on inhaled steroids alone or for those patients with symptoms sufficiently challenging to warrant the potential extra risk associated with use of the agents.

Systemic Adrenergic Agonists

Systemic administration of adrenergic agonists for asthma was used more frequently in the past. Oral, intravenous (IV), or subcutaneous administration of β -specific or nonspecific adrenergic agonists is now reserved for rescue therapy. The mechanism of action of systemically administered adrenergic agonists is the same as it is for inhaled agents. Binding of the drug to the β_2 -adrenergic receptor on smooth muscle cells in the airway is responsible for the bronchodilatory effects. Specifically, β_2 -receptor stimulation induces a stimulatory G protein to convert adenosine triphosphate to cAMP and in turn reduces intracellular calcium release and alters membrane potential.

Terbutaline can be given orally, subcutaneously, or intravenously; albuterol (salbutamol) can be given intravenously; and epinephrine is usually given subcutaneously or intravenously. Regardless of the route of administration, all three will produce bronchodilation. Comparison of IV and inhaled formulations of terbutaline failed to demonstrate any difference in bronchodilation and, with the propensity for IV formulations to cause side effects, inhaled therapy should be considered the first-line treatment.^{24,25} This principle not only applies to terbutaline but all β -adrenergic agonists that are available in IV and inhaled forms. If inhaled therapy is not readily available or if inhaled therapy is maximized and symptoms persist, then subcutaneous epinephrine or terbutaline can be administered with improvement in symptoms and spirometry values.²⁶ In summary, subcutaneous or IV β agonists should be reserved only for rescue therapy.

The side effect profile of systemic adrenergic agonists is similar to the side effect profile for inhalational adrenergic agonists. The most common side effects are tremor and tachycardia. Arterial oxygen tension can be transiently decreased and hyperglycemia, hypokalemia, and hypomagnesemia can also be present. Escalating oral, subcutaneous, or IV doses can be associated with a greater incidence of side effects for the same degree of bronchodilation compared to inhaled β -adrenergic agonists.

Inhaled Cholinergic Antagonists

The use of anticholinergics for maintenance therapy and treatment of acute exacerbations in obstructive airway diseases is common. The parasympathetic nervous system is primarily responsible for bronchomotor tone and inhaled anticholinergics act on muscarinic receptors in the airway to reduce tone. The use of inhaled anticholinergics (see **Table 25.1**) in COPD as maintenance and rescue therapy is considered standard treatment.²⁷ Anticholinergics are not used for maintenance therapy in asthma and are only recommended for use in acute exacerbations.²⁸ The targets of therapy for anticholinergics are the muscarinic receptors located in the airway. There are three subtypes of muscarinic receptors found in the human airway.²⁹ Muscarinic 2 (M2) receptors are present on postganglionic cells and are responsible for limiting production of acetylcholine and protect against bronchoconstriction. The M2 is not the target of inhaled anticholinergics but is antagonized by them. Muscarinic 1 (M1) and M3 receptors are responsible for bronchoconstriction and mucus production and are the targets of inhaled anticholinergic therapy. Acetylcholine binds to the M3 and M1 receptors and causes smooth muscle contraction via increases in cyclic guanosine monophosphate (cGMP) or by activation of a G protein.²⁹ The G protein activates phospholipase C to produce inositol triphosphate, which causes release of calcium from intracellular stores and activation of myosin light chain kinase causing smooth muscle contraction. Anticholinergics inhibit this cascade and reduce smooth muscle tone by decreasing release of calcium from intracellular stores.

There are two inhaled anticholinergics specifically approved for the treatment of obstructive airway diseases. Ipratropium is classified as a short-acting anticholinergic and is commonly used as maintenance therapy for COPD and as rescue therapy for both COPD and asthmatic exacerbations. It is not indicated for the routine management of asthma. Patients treated with ipratropium experience an increase in exercise tolerance, decrease in dyspnea, and improved gas exchange. Tiotropium is the only long-acting anticholinergic available for COPD maintenance therapy. Tiotropium has been shown to reduce COPD exacerbations, respiratory failure, and all-cause mortality.³⁰

Inhaled anticholinergics are poorly absorbed and therefore serious side effects are uncommon. Most commonly, patients experience dry mouth, urinary retention, and can experience pupillary dilation and blurred vision if the eyes are inadvertently exposed to the drug. Some initial data suggested an increase in cardiovascular and stroke complications with tiotropium; however, additional studies did not consistently demonstrate these complications. In general, anticholinergics are safe and effective treatment for patients with obstructive airway diseases.

Systemic Cholinergic Antagonists

The systemically administered anticholinergics atropine and glycopyrrolate act via the same mechanisms as inhaled anticholinergics. Although these anticholinergics can be administered by IV or inhalation, significant systemic absorption occurs, and their use is generally limited by side effects. Atropine, in particular, is limited in use because of its tertiary ammonium structure. It has a tendency to cause tachycardia, gastrointestinal upset, blurred vision, dry mouth, and central nervous system effects secondary to its ability to cross the blood–brain barrier. Glycopyrrolate has a quaternary ammonium structure and is insoluble in lipids, similar to ipratropium and tiotropium, and has fewer systemic side effects than atropine. An IV glycopyrrolate is also clinically limited in use secondary to side effects.³¹ Glycopyrrolate has been studied as inhaled therapy, however, and is an effective bronchodilator with an intermediate duration of action.^{32–35} Clinically, it has never been popular as a mainstay of therapy for obstructive airway diseases.

Influence of Inflammation on the Airway

Asthma and COPD, the most common obstructive airway diseases, have a component of inflammation as part of their pathogenesis. Although inflammation is a common pathogenesis, the characteristics and prominent cellular elements involved in the inflammatory process for each disease are distinct.³⁶ In COPD, neutrophils, macrophages, CD8⁺ T lymphocytes, and eosinophils are more prominent in the inflammatory composition. In asthma, eosinophils play a more prominent role followed by mast cells, CD4⁺ T lymphocytes, and macrophages in the inflammatory composition. Inflammatory cell types present in sputum, biopsy specimens, and bronchoalveolar lavage fluid can help predict the response to antiinflammatory therapy. For example, eosinophilia in induced sputum of a patient presenting with a COPD exacerbation predicts an increase in steroid responsiveness.^{37,38} Patients presenting to the operating room with obstructive airway diseases have a high likelihood of taking one of the antiinflammatory therapies in **Table 25.2** for control of their disease.

TABLE 25.2

Pharmacologic influence on inflammation^a

Inhaled corticosteroids	Leukotriene modifiers	Mast cell stabilizers	Methylxanthines
Monotherapy	Antagonists		
Beclomethasone	Montelukast	Cromolyn sodium	Theophylline
Budesonide	Zafirlukast	Nedocromil	Aminophylline
Ciclesonide	Pranlukast (not in United States)		
Flunisolide	Inhibitors		
Fluticasone	Zileuton		
Mometasone			
Triamcinolone			

Combination therapy			
Budesonide/formoterol			
Fluticasone/salmeterol			

^aReprinted by permission from Springer: Bailey C, Wojciechowski PJ, Hurford WE. Pharmacology of the airways. In: Slinger P, ed. *Principles and Practice of Anesthesia for Thoracic Surgery*. 2nd ed. Cham, Switzerland: Springer; 2019:151-164. Copyright © 2019 Springer Nature Switzerland AG.

Inhaled Corticosteroids

In the treatment of asthma, the use of inhaled corticosteroids (ICS) reduces the inflammatory changes associated with the disease, thereby improving lung function and reducing exacerbations that result in hospitalization and death.³⁹⁻⁴¹ On the contrary, the use of ICS as monotherapy in COPD is discouraged. In COPD, ICS are used as a part of combination therapy along with long-acting β-adrenergic agonists (LABA). The combination of drugs acts synergistically and is useful for reducing inflammation. Currently, combination therapy of ICS and LABA is recommended for use in severe to very severe COPD.⁴² The glucocorticoid receptor α located in the cytoplasm of airway epithelial cells is the primary target of ICS.^{43,44} Passive diffusion of steroids into the cell allows for binding of the steroid ligand to glucocorticoid receptor α, dissociation of heat shock proteins, and subsequent translocation to the nucleus. The complex can bind to promoter regions of DNA sequences and either induce or suppress gene expression. Additionally, the steroid-receptor complex can interact with transcription factors already in place, such as the ones responsible for proinflammatory mediators, without binding to DNA and repress expression of those genes. The steroid-receptor complex also can affect chromatin structure by association with transcription factors that influence the winding of DNA around histones, reducing access of RNA polymerase and other transcription factors, and thus reducing expression of inflammatory gene products.

The ICS are used in asthma as part of a multimodal treatment regimen and are added to a therapeutic regimen when there is an increase in severity or frequency of asthma exacerbations. There is good evidence to show that ICS can reduce both hospitalizations and death in asthma. The use of ICS in COPD is limited to use in severe to very severe COPD and in combination with LABA. Although no improvement in mortality has been consistently demonstrated with combination therapy (ICS/LABA), there are reported improvements in health status and lung function along with a reduction in exacerbations.

Side effects have been reported with the use of ICS in asthma and COPD. A meta-analysis reported an increase in pneumonia and serious pneumonia but not deaths when ICS was used in the treatment of COPD.⁴⁵ Other reported side effects in COPD and asthma include oropharyngeal candidiasis, pharyngitis, easy bruising, osteoporosis, cataracts, elevated intraocular pressure, dysphonia, cough, and growth retardation in children. As with any pharmacotherapy, the risks and benefits of therapy must be weighed, and the patient must be carefully monitored for adverse effects. This is especially true with the use of ICS in obstructive lung diseases.

Systemic Corticosteroids

Systemic corticosteroids given in IV or oral form are used for treatment of asthma and COPD exacerbations. The mechanism of action is the same as it is for ICS, activation or suppression of gene products at a transcriptional level and alteration of chromatin structure. Patients who are hospitalized with a COPD exacerbation will typically receive IV corticosteroids to suppress any inflammatory component that may be contributing to the flare up. A study done at the Veterans Affairs medical centers in the United States published in 1999 reported that corticosteroid therapy shortened hospital length of stay and improved forced expiratory volume in 1 second versus placebo.⁴⁶ The study also compared a 2-week regimen versus an 8-week regimen of corticosteroids and found no difference, concluding that the duration of therapy should last only 2 weeks. In asthma, corticosteroids are recommended for exacerbations that are either severe, with a peak expiratory flow of less than 40% of baseline, or a mild to moderate exacerbation with no immediate response to short-acting β-adrenergic agonists. The recommended duration of therapy is 3 to 10 days without

tapering. Alternatively, some patients with asthma and COPD will be receiving long-term oral corticosteroid therapy because their disease is difficult to manage. Side effects of systemic corticosteroids are well described and numerous. Hypertension, hyperglycemia, adrenal suppression, increased infections, cataracts, dermal thinning, psychosis, and peptic ulcers are reported complications of corticosteroid therapy.⁴⁷

Leukotriene Modifiers

Leukotriene modifiers are used for the treatment of asthma. They are prescribed primarily for long-term control in addition to short-acting β -adrenergic agonists or in conjunction with ICS and short-acting β agonists. Leukotriene modifiers are taken by mouth, produce bronchodilation in hours, and have maximal effect within days of administration. Their role in the management of COPD is not defined.⁴⁸ Arachidonic acid is converted to leukotrienes via the 5-lipoxygenase pathway.⁴⁹ Leukotrienes C₄, D₄, and E₄ are the end products of the pathway and cause bronchoconstriction, tissue edema, migration of eosinophils, and increased airway secretions. Leukotriene modifiers come in two different varieties: leukotriene receptor antagonists and leukotriene inhibitors.⁴⁹ The leukotriene inhibitor zileuton antagonizes 5-lipoxygenase inhibiting the production of leukotrienes.

Leukotriene modifiers improve lung function, reduce exacerbations, and are used as long-term asthma therapy.^{50,51} Clinical trials have reported that ICS are superior to leukotriene modifiers for long-term control and should be the first-line choice.^{52,53} Leukotriene modifiers provide an additional pharmacologic option for the control of asthma. Addition of leukotriene modifiers to ICS will improve control of symptoms of asthma as opposed to ICS alone.⁵⁴

Leukotriene antagonists are usually well tolerated without significant side effects. Links between Churg-Strauss syndrome and the use of leukotriene antagonists have been reported, but it is not clear whether these reports reflect unmasking of a preexisting condition or whether there is a direct link between the two. Zileuton is known to cause a reversible hepatitis in 2% to 4% of patients.

Mast Cell Stabilizers

Cromolyn sodium and nedocromil are the two agents in this category that are used in the treatment of asthma. These agents are delivered by powder inhaler and are not first-line therapy for asthma. They do provide an alternative treatment when the control of asthma is not optimal on other conventional therapies. Cromolyn sodium and nedocromil stabilize submucosal and intraluminal mast cells.⁵⁵ These drugs interfere with the antigen-dependent release of mediators, such as histamine and slow-reacting substance of anaphylaxis, that cause bronchoconstriction, mucosal edema, and increased mucus secretion.

Systematic reviews of the available literature and consensus statements favor the use of ICS over cromolyn sodium or nedocromil as first-line agents to control symptoms of asthma.⁵⁶ Alternatively, cromolyn sodium and nedocromil may be used as preventative treatment before exercise or known allergen exposure causing symptoms of asthma. There are no major side effects reported with the use of cromolyn sodium and nedocromil. The most commonly reported side effects are gastrointestinal upset and coughing or irritation of the throat.

Methylxanthines

The role of theophylline, a methylxanthine, has changed since the introduction of ICS and LABA. Theophylline was a common choice for the control of asthma and COPD because of its bronchodilatory and antiinflammatory effects.⁵⁷ Currently, theophylline is recommended only as an alternative therapy and is not a first-line choice for asthma or COPD.^{58,59} Theophylline acts via multiple pathways causing improvement in symptoms in obstructive lung diseases. Theophylline is a nonselective inhibitor of phosphodiesterase and increases levels of cAMP and cGMP causing smooth muscle relaxation. Antagonism of the A₁ and A₂ adenosine receptors also causes smooth muscle relaxation via inhibition of the release of histamine and leukotrienes from mast cells, another reported action of theophylline. In asthma, theophylline reduces the number of eosinophils in bronchial specimens and, in COPD, reduces the number neutrophils in sputum, having an antiinflammatory effect in both conditions. In addition, theophylline activates histone deacetylase

and reduces the expression of inflammatory genes. Theophylline and aminophylline are reported to improve diaphragmatic function; however, data have not demonstrated this effect consistently.⁶⁰

Theophylline has been relegated to an alternative therapy in both asthma and COPD. This has occurred largely because of its significant side effect profile and the subsequent need for monitoring of blood level. Patients who are already on an ICS and an LABA and still have symptoms may benefit from the addition of theophylline, especially if leukotriene modifiers and other alternatives are not tolerated. Theophylline can cause significant and life-threatening side effects if not dosed carefully and monitored appropriately. Side effects tend to be more prominent when blood levels exceed 20 mg/L. The most common side effects include headache, nausea, vomiting, restlessness, abdominal discomfort, gastroesophageal reflux, and diuresis. The most significant side effects include seizures, cardiac arrhythmias, and death. Adverse effects from theophylline may be avoided if the clinician follows the patient carefully, monitors blood levels regularly, and educates the patient on the signs and symptoms of overdose.

Combined Pharmacologic Therapy of Asthma

Patients with chronic asthma are commonly treated with combination therapy designed to interrupt the bronchoconstrictive pathology by different pharmacologic methods. There is some synergism between antiinflammatory agents and direct acting bronchodilators. A six-step program for managing asthma in adults is outlined in **Table 25.3**, and patients move up or down the steps depending on the severity of their symptoms.

TABLE 25.3					
A stepwise approach to managing asthma in adults ^a					
Step 1	Step 2	Step 3	Step 4	Step 5	Step 6
Inhaled short-acting β_2 -agonist as needed	Low-dose inhaled steroid	Low-dose inhaled steroid	Medium-dose inhaled steroid	High-dose inhaled steroid	High-dose inhaled steroid
	Inhaled short-acting β_2 -agonist as needed	Inhaled long-acting β_2 -agonist	Inhaled long-acting β_2 -agonist	Inhaled long-acting β_2 -agonist	Inhaled long-acting β_2 -agonist
	Alternatives: Leukotriene antagonist or mast cell stabilizers		(Combined inhalers)	Monoclonal antibody (?) (allergic asthma)	Monoclonal antibody (?)
					Oral steroids

Abbreviations: ?, under investigation.

^aBased on information from Managing Asthma in Youths >12 years and Adults. UpToDate Online medical information resource, Wolters Kluwer, accessed June 2019.

Influence of Anesthetics on the Airways

Volatile Anesthetics

Volatile anesthetics have a host of effects on the respiratory system. Volatile anesthetics reduce bronchomotor tone, and all commonly used volatile anesthetics (**Table 25.4**), except desflurane and nitrous oxide, produce a degree of bronchodilatation that may be helpful in patients with obstructive lung disease or in patients who experience any degree of bronchoconstriction.⁶¹ Rooke and colleagues⁶² in 1997 reported that sevoflurane produced a greater reduction in respiratory system resistance than isoflurane or halothane. Volatile anesthetics likely induce bronchodilation by decreasing intracellular calcium, partly mediated by an increase in intracellular cAMP and by decreasing the sensitivity of calcium mediated by protein kinase C.⁶³ The effect is seen to a greater degree in distal airway smooth muscle secondary to the T-type voltage-dependent calcium channel, which is sensitive to volatile anesthetics.⁶⁴

TABLE 25.4**Anesthetics with a favorable influence on bronchomotor tone^a**

Volatile anesthetics	Intravenous anesthetics
Isoflurane	Propofol
Sevoflurane	Ketamine
Halothane	Midazolam

^aReprinted by permission from Springer: Bailey C, Wojciechowski PJ, Hurford WE. Pharmacology of the airways. In: Slinger P, ed. *Principles and Practice of Anesthesia for Thoracic Surgery*. 2nd ed. Cham, Switzerland: Springer; 2019:151-164. Copyright © 2019 Springer Nature Switzerland AG.

Volatile anesthetics are administered to provide amnesia and blunt the response to surgical stimulation but can be of use in patients who have obstructive airway diseases or experience bronchoconstriction in the operating room. Multiple case reports provide examples of how volatile agents were used solely for the treatment of status asthmaticus.⁶⁵⁻⁶⁸ The main concern with the use of volatile anesthetics is the rare occurrence of malignant hyperthermia. Hypotension can also be a concern with volatile anesthetics; however, the blood pressure is usually easily restored with small amounts of vasopressors. Deep levels of anesthesia associated with high concentrations of volatile anesthetics may be undesirable, and prolonged administration outside the operating room is problematic.

Intravenous Anesthetics

The IV anesthetics can decrease bronchomotor tone when used for induction or IV anesthesia in the operating room. Ketamine, propofol, and midazolam (see **Table 25.4**) have relaxant effects on airway smooth muscle.⁶⁹ Etomidate and thiobarbiturates do not affect bronchomotor tone to the same extent.⁷⁰ The choice of IV anesthetics for induction and maintenance of anesthesia may be important for a patient with reactive airway disease. The mechanism of reduction of bronchomotor tone for the IV anesthetics is largely unknown. Ketamine is thought to have a direct relaxant effect on smooth muscle.⁷¹ Propofol is thought to reduce vagal tone and have a direct effect on muscarinic receptors by interfering with cellular signaling and inhibiting calcium mobilization.^{72,73} Propofol may be the most effective anesthetic for preventing reflex bronchoconstriction during anesthesia. In a randomized trial, children at risk had fewer adverse respiratory events during induction of anesthesia with IV propofol than inhaled sevoflurane.⁷⁴

Choosing an agent such as propofol or ketamine can be beneficial in patients with bronchospasm or obstructive airway disease. The use of these IV agents for induction or maintenance of anesthesia over other agents can be useful in minimizing the intraoperative effects of bronchospasm. Although each of the IV anesthetics carries a unique side effect profile, the major effects are not related to the airway. The use of ketamine is associated with increased salivation and coadministration of a small dose of anticholinergic can attenuate secretion production. Propofol is associated with hypotension that usually is easily corrected with vasopressors. A schematic representation of the anatomy of the bronchus and the sites of actions of various pharmacologic agents used to treat asthma is shown in **Figure 25.1**.

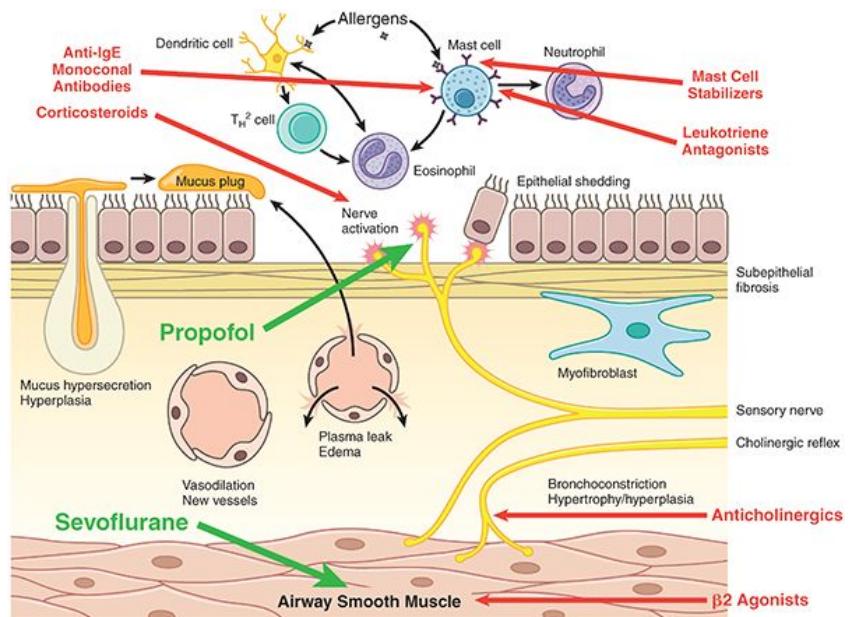


FIGURE 25.1 A diagram of the histology and pharmacology of a section of the asthmatic bronchus. The airway and epithelium are at the top, and the bronchial smooth muscle is at the bottom. Antiinflammatory agents act primarily at the level of the respiratory epithelium, whereas bronchodilators act at the level of the airway smooth muscle. Abbreviation: IgE, immunoglobulin E.

Local Anesthetics

Local anesthetics are primarily used to suppress coughing and blunt the hemodynamic response to tracheal intubation.^{75,76} Although animal models have demonstrated some ability of local anesthetics to relax bronchial smooth muscle, in clinical practice, the use of local anesthetics as pure bronchodilators is limited by toxicity and the ready availability of more potent bronchodilators such as short-acting β -adrenergic agonists.

Influence of Adjunctive Agents on the Airway

Helium (administered as a mixture of helium and oxygen [Heliox]) has the advantage of having a low Reynolds number and less resistance during turbulent airflow especially in large airways (see [Chapter 24](#)). A trial in patients with COPD exacerbations failed to demonstrate a statistically significant reduction in the necessity for endotracheal intubation in patients treated with noninvasive ventilation and helium-oxygen mixtures.⁷⁷ Helium-oxygen mixtures may be useful as short-term temporizing therapy to decrease the work of breathing in patients with upper airway obstruction. The use of helium-oxygen mixtures is limited by a progressive reduction in efficacy at higher inspired oxygen concentrations.

Antihistamines: Histamine release from mast cells and basophils is responsible for airway inflammation and bronchoconstriction in asthma.⁷⁸ Antihistamines are not standard therapy for asthma, but the use of antihistamines and leukotriene modifiers for allergen-induced bronchoconstriction has shown promise for diminishing the early and late responses to allergens.^{78,79} Patients who have allergen-induced asthma or patients who experience an allergic reaction in the operating room may benefit from antihistamines to attenuate the role that histamine plays in bronchoconstriction.

Magnesium sulfate is not standard therapy for asthma exacerbations. Magnesium sulfate is thought to produce additional bronchodilation when given in conjunction with standard therapy for asthma exacerbations. Currently, IV magnesium therapy is reserved as an alternative therapy when the patient has not responded to standard therapy.⁸⁰ The combination of nebulized magnesium sulfate and β -adrenergic agonists have also been studied and show potential benefit in asthma exacerbations.⁸¹ Overall, magnesium sulfate, IV

or nebulized, is not a first-line therapy for asthma exacerbations and should be reserved for situations when the patient is not responding to conventional therapy.

Pharmacology of the Pulmonary Circulation

Patients with pulmonary hypertension (PHTN) are high-risk candidates for both cardiac and noncardiac surgery. They have poor cardiorespiratory reserve and are at risk for having perioperative complications including pulmonary hypertensive crises with resultant heart failure, respiratory failure, and dysrhythmias.^{82,83} Anesthetic management of these patients can be complex and challenging. Drugs affecting the pulmonary vascular bed are routinely administered during anesthesia, and their effects are of particular interest in patients with PHTN. Reducing the consequences of an elevated pulmonary vascular resistance (PVR) and the resulting right ventricular dysfunction should be considered as the primary goal of therapy with pulmonary vasodilators. Owing to the contractile properties of the naive right ventricle, attempts at improving its contractility are generally not effective. Therefore, principles of management of PHTN center on reducing right ventricular afterload while preserving coronary perfusion by avoiding reductions in systemic blood pressure.⁸⁴

Anesthetic Drugs

Evaluating the effects of anesthetic drugs on the pulmonary vasculature is challenging. In clinical practice and research, these drugs are rarely administered in isolation. Their administration can lead to concurrent changes in nonpulmonary hemodynamic parameters such as cardiac output (CO) that ultimately affect pulmonary artery pressure (PAP). An increase in PAP may be the result of increased PVR, increased CO, or an increase in left atrial pressure (LAP) ($PAP = [PVR \times CO] + LAP$). In addition, general anesthesia involves manipulation of variables that affect PVR, including fraction of inspired oxygen (FoI_2), carbon dioxide, and positive pressure ventilation.

Ketamine

Historically, ketamine has occupied a controversial position in anesthesia for patients with PHTN. Despite its current widespread use in these challenging patients, it has been classically taught that ketamine causes pulmonary vasoconstriction and should be used with extreme caution in this group. The mechanism of action of ketamine is not fully elucidated. It is an *N*-methyl-D-aspartic acid receptor antagonist and also binds to opioid receptors and muscarinic receptors.⁸⁵ It appears to stimulate release as well as inhibit neuronal uptake of catecholamines, which may account for its cardiotonics and bronchodilatory effects. Some animal studies have shown an endothelium-independent vasodilatory response to ketamine in the pulmonary bed.

The effects of ketamine on the human pulmonary vasculature appear to be complex and the clinical literature reveals a vast heterogeneity in regard to results. Factors known to affect pulmonary vasoreactivity such as FoI_2 , carbon dioxide, presence of PHTN, and presence of premedicants are not reported or acknowledged in many studies. The hemodynamic effects of a bolus of ketamine can be attenuated or abolished with premedicants such as droperidol, dexmedetomidine, or benzodiazepines.⁸⁶ Early study of the drug's hemodynamic profile in adult patients showed increases of PAP and PVR in the range of 40% to 50%. This, combined with increases in variables contributing to myocardial oxygen consumption, raised concern about the use of ketamine in patients with coronary artery disease and PHTN.

A systematic review of the use of ketamine in children with congenital heart disease and/or PHTN found that PAP, PVR, and heart rate did not change significantly with the administration of ketamine.⁸⁷ In another pediatric study, ketamine maintained pulmonary to systemic blood flow and did not affect pulmonary pressure or resistance in children with intracardiac shunt undergoing cardiac catheterization. Propofol, on the other hand, decreased systemic vascular resistance (SVR) leading to increased right to left shunting.⁸⁸ In adult patients undergoing one-lung ventilation (OLV) for lung resection, ketamine did not significantly increase PAP or PVR compared to enflurane. Other case reports highlight the value of the relative cardiostability of the drug in patients with minimal cardiorespiratory reserve.^{89,90} Many clinicians incorporate this drug into their routine inductions for patients with severe PHTN (eg, pulmonary endarterectomy or lung

transplantation). The advantages, in particular maintenance of stable hemodynamics and coronary perfusion pressure, seem to outweigh the potential disadvantages.

Propofol

Propofol is commonly used in anesthesia, including for patients with PHTN. It is frequently used to maintain anesthesia during and after lung transplantation. The effects of propofol are thought to be primarily mediated by γ -aminobutyric acid receptors. The concerning hemodynamic effect of propofol in the context of PHTN is a decrease in SVR, which can not only have effects on intracardiac shunting, if present, but also can lead to decreased coronary artery perfusion of the right ventricle and resultant right ventricular dysfunction. In regard to direct effects on the pulmonary vasculature, animal studies have shown that during increased tone conditions in the pulmonary vasculature, propofol may act as a pulmonary vasoconstrictor.⁹¹ Propofol has also been shown to interfere with acetylcholine-induced pulmonary vasodilation in dogs.⁹² On the other hand, in isolated pulmonary arteries from human and chronically hypoxic rats, etomidate and to a lesser extent propofol showed vessel relaxation.⁹³ The clinical significance of these contradictory results is unknown.

Etomidate

Etomidate is an imidazole that mediates its clinical actions primarily at γ -aminobutyric acid A receptors. As mentioned earlier, it appears to have vasorelaxant properties in isolated pulmonary arteries. Its major attribute as an induction agent is its stable hemodynamic profile. In patients with cardiac disease, an induction dose of etomidate increased mean arterial pressure (MAP), decreased SVR, and decreased PAP.⁹⁴ In pediatric patients without PHTN presenting for cardiac catheterization, there was no significant change in any hemodynamic parameters after induction with etomidate.⁹⁵

Opioids

Opioids seem to have little to no deleterious effects on the pulmonary vascular system. In anesthetized cats, administration of morphine, fentanyl, remifentanil, and sufentanil caused a vasodilatory response under elevated tone conditions in isolated lobar artery.⁹⁶ The mechanism seems to involve histamine- and opioid-mediated receptor pathways. Clinical experience would echo the cardiostability of judicious narcotic administration in hemodynamically fragile patients.

Volatile Anesthetics

At clinically relevant concentrations, modern volatile anesthetics likely have little to no direct vasodilating effect on the pulmonary vasculature. In pigs, sevoflurane administration depressed right ventricular function with no change in PVR.⁹⁷ This suggests that the decreases in PAP observed with volatile anesthetics may partially occur secondary to the decreases in CO seen with these agents. Nitrous oxide is typically avoided in patients with PHTN as it is believed to cause pulmonary vasoconstriction, perhaps via release of catecholamines from sympathetic nerves supplying the pulmonary vasculature. In patients with mitral stenosis and PHTN presenting for cardiac surgery, administration of nitrous oxide after fentanyl anesthesia (7.5-10 μ g/kg) increased PVR, PAP, and cardiac index.⁹⁸ However, a subsequent study showed that in the presence of high-dose fentanyl (50-75 μ g/kg), 70% nitrous oxide is actually associated with a decrease in PAP and CO in patients with secondary PHTN, with no echocardiographic changes in right ventricular function.⁹⁹

Neuromuscular Blockers

Pancuronium increases PAP in dogs with lung injury.¹⁰⁰ It is theorized to do so indirectly by increases in CO and directly by increasing PVR, possibly by its antagonist actions at muscarinic receptors in the pulmonary vasculature. Rocuronium, cisatracurium, and vecuronium have little to no effect on most cardiac indices in patients undergoing coronary artery bypass graft.¹⁰¹

Magnesium

Magnesium is a vasodilator in both the systemic and pulmonary circulations. The mechanism of action of magnesium's effects on vasodilation is likely through its effects on membrane channels involved in calcium flux and through its action in the synthesis of cAMP. It would appear to be an important cofactor for endothelial-dependent pulmonary vasodilation. It has been used successfully to wean NO in PHTN.¹⁰² Increasing doses of magnesium in piglets with acute embolic PHTN decreased mPAP, increased CO, and decreased PVR.¹⁰³ Magnesium has been used to treat persistent PHTN of the newborn, but controversy surrounds its use.

Regional Analgesia

Pain can increase PVR.¹⁰⁴ Perioperative thoracic epidural analgesia (TEA) is commonly used in abdominal and thoracic surgery. The TEA may decrease PAP through decreases in CO or via attenuation of the pulmonary sympathetic outflow. In pigs, TEA depresses right ventricular function in acute PHTN.¹⁰⁵ Unilateral thoracic paravertebral block with lidocaine has been shown to decrease myocardial contractility up to 30% and significantly decrease systemic pressure; an effect that may be attenuated by epinephrine. In general, the potential benefits of regional anesthesia in thoracoabdominal surgery typically outweigh the risks of hypotension and right ventricular dysfunction. As with most anesthetic interventions in patients with PHTN, careful titration and monitoring is paramount. A few reports illustrate successful use of epidural analgesia in this patient population.¹⁰⁶

Vasopressors and Inotropes

Vasopressors and inotropes are commonly required during anesthesia to counteract the effects of cardiodepressant and vasodilating drugs. Treatment of hypotension in these patients can be difficult to manage given the typical cautious fluid administration most patient populations.

The innervation and receptor content of the pulmonary vasculature is complex. Neurotransmitter receptors in this system include those from the adrenergic, cholinergic, and dopaminergic families as well as histamine, serotonin, adenosine, purines, and peptides. The pulmonary vasculature's response to sympathetic activation will generally result in an increase in PVR. In human pulmonary artery, administration of acetylcholine induces pulmonary relaxation.¹⁰⁷

The response of the pulmonary system to exogenous vasopressor administration is dependent on the clinical situation. Consequently, results of studies are heterogeneous. In anesthetized dogs without PHTN, dopamine, epinephrine, norepinephrine, and phenylephrine all increase PAP to varying degrees by varying mechanisms but with no drug is there a significant increase in PVR.¹⁰⁸ Dopamine does not increase PVR after lung transplantation in pigs.¹⁰⁹ In anesthetized patients with chronic secondary PHTN undergoing cardiac surgery, both norepinephrine and phenylephrine increase PAP and pulmonary vascular resistance index (PVRI) with minimal change in cardiac index.¹¹⁰ Within the clinically relevant MAP target in this study, norepinephrine decreased the mPAP-to-MAP ratio, but phenylephrine did not, suggesting it may be a better choice in this patient cohort. In a dog model of acute PHTN, however, phenylephrine restored perfusion to the ischemic right ventricle and therefore increased CO.¹¹¹ This is a relevant observation, as it illustrates the importance of coronary artery perfusion in the setting of right ventricular strain and that maintenance of systemic pressure by whatever method may be the most important principle in this subset of patients.

Vasopressin has also been studied. In a chronic hypoxic rat model, vasopressin administration resulted in a V1 receptor-mediated pulmonary vasodilation.¹¹² In an acute PHTN model in dogs, vasopressin increased PVR and resulted in a substantial decrease in right ventricular contractility.¹¹³ Human studies of effects of vasopressin on the pulmonary vasculature are limited. Vasopressin has been used successfully after cardiac surgery in patients with PHTN and resistant hypotension.¹¹⁴ The use of vasopressin to treat acute right ventricular failure in patients with IPPH has been described in obstetric anesthesia.¹¹⁵

Pulmonary Vasodilators

Pulmonary vasodilators are typically employed to improve right ventricular function in the setting of PHTN or in an effort to enhance regional pulmonary blood flow and improve intrapulmonary shunt. In the acute care setting, however, it is these agents' pulmonary vasodilatory effects that are being exploited. In general, parenteral and oral vasodilators are hampered by their relatively nonselective actions in the pulmonary vascular bed. In addition to their hypotensive systemic hemodynamic effects, their use may also lead to perfusion of underventilated alveoli, worsen intrapulmonary shunt, and, in turn, worsen oxygenation. The ideal pulmonary vasodilator should have a rapid onset of action and a short half-life and produce regional pulmonary vasodilation. This would avoid systemic hypotension and the potential adverse effects on ventilation-perfusion matching that limit the use of systemic agents in critically ill patients. In this regard, inhaled vasodilators are attractive as they preferentially dilate ventilated alveoli and have less systemic effects.

Nitric Oxide

Inhaled nitric oxide (iNO) is preferentially delivered to ventilated lung units leading to improved perfusion to alveoli that are able to participate in gas exchange. This "selective effect" leads to a decrease in intrapulmonary shunt. Medical grade NO may be administered either noninvasively (via a facemask) or through a ventilator circuit. If administered through a circuit, a device is used that can regulate the concentration of NO and monitor levels of nitrogen dioxide—a by-product of NO when it combines with oxygen ([Figure 25.2](#)). The iNO is approved for infants with respiratory distress syndrome. This approval stems from large prospective placebo-controlled studies demonstrating that NO reduced the need for extracorporeal membrane oxygenation and reduced the requirement for oxygen therapy following intensive care unit discharge.^{[116](#)} Although there is controversy about a dose-response relationship for NO and pulmonary vasodilation, the typical dose ranges from 10 to 40 ppm. Methemoglobin levels need to be monitored when NO is administered for more than 24 hours. Heart and lung transplantation represent two distinct areas where acute pulmonary vasodilation has strong theoretic benefit as it relates to improving acute right ventricular failure and attenuating reperfusion injury, respectively. The acute right ventricular failure complicating heart transplantation may be attenuated with the use of an inhaled pulmonary vasodilator. Although several studies suggest that NO may be useful preoperatively in risk-stratifying patients scheduled for cardiac transplant, only case series support the use of iNO to reverse the right ventricular dysfunction following cardiac transplant. However, based on clinical experience, iNO has become a standard of care in many transplant centers. The beneficial immune-modulating effects of iNO in addition to its vasodilating properties were felt to be responsible for preliminary studies of using iNO to prevent primary graft dysfunction (PGD) after lung transplantation.^{[117](#)} Although a randomized clinical trial failed to show benefit in preventing PGD, it is commonly used to treat the hypoxemia and PHTN seen in established, severe PGD.^{[118](#)} Owing to the inherent cost of using iNO, other pulmonary vasodilators have been evaluated.



FIGURE 25.2 A commercial device for administration of nitric oxide (NO) via a ventilator circuit. The NO is administered into the inspiratory limb of the anesthesia circuit close to the connection to the endotracheal tube. The concentration of the toxic metabolite nitrogen dioxide is monitored in the circuit via an attachment to the expiratory limb (circled in the photograph).

In nontransplant thoracic surgery, NO has been studied as a potential treatment for the gas exchange abnormalities associated with OLV. Its effects are controversial, but it would appear that it exerts its maximal benefits in patients with elevated PVRI and the poorest gas exchange before administration.¹¹⁹ NO can be quickly delivered via the circuit of anesthetic or intensive care ventilator; however, it is expensive and not widely available.

Prostaglandins

Prostanoids induce relaxation of vascular smooth muscle, inhibit growth of smooth muscle cells, and are powerful inhibitors of platelet aggregation.¹²⁰ Inhaled prostanoids involve an aerosol delivery mechanism that is attached by a nebulizer to the ventilator circuit ([Figure 25.3](#)). Treatment may be limited by inefficiencies in aerosolization. Owing to the short half-life of epoprostenol, the drug must also be continuously nebulized.¹²¹ As a result, changes of dose delivery with alterations in ventilator volumes, $\text{F}\text{I}\text{O}_2$, airway pressures, and solvent evaporation may be challenging. The synthetic prostanoids, treprostinil and iloprost, hold promise as inhaled vasodilators in that they may only require intermittent administration. When nebulized, prostanoids can lead to similar improvements in oxygenation and pulmonary pressures as compared to iNO. A crossover study compared iNO to inhaled prostaglandins in patients after lung ($n = 19$) or heart ($n = 6$) transplant. In this acute hemodynamic study, there was no significant difference in hemodynamics or oxygenation between agents.¹²² Prostacyclin can be delivered by nebulizer into a ventilator circuit at a starting dose of 50 ng/kg per minute and clinical effects should be evident within 10 minutes (see [Figure 25.3](#)).¹²³



FIGURE 25.3 Prostacyclin can be delivered via continuous nebulization into an intensive care (pictured here) or an anesthesia ventilator circuit for specific pulmonary vasodilation.

Use of IV prostaglandins during OLV results in a decrease in both systemic and pulmonary pressures and either no change or a decrease in PaO_2 . Selective infusion of prostaglandin into the pulmonary artery of the ventilated lung in a human model during OLV resulted in stable systemic pressure and a reduction in PVR and increase in PaO_2 .¹²⁴ However, this route of administration is not practical in routine thoracic anesthesia practice. Inhaled prostacyclin decreases PVRI and PAP with maintenance of favorable systemic pressures but does not change PaO_2 during OLV.¹²⁵

Both iNO and prostaglandins have been shown to affect platelet function. This could theoretically contribute to perioperative bleeding during large surgeries such as lung transplantation and is a concern in regard to neuraxial analgesia. The clinical relevance of platelet inhibition with these inhaled agents is unknown. In cardiac surgery patients, laboratory confirmation of platelet dysfunction with inhaled prostacyclin did not correlate with chest tube losses.¹²⁶ Also, in an obstetrical patient with PHTN on IV prostacyclin, conversion to inhaled prostacyclin allowed for a successful labor epidural placement with no complications.¹²⁷

Phosphodiesterase Inhibitors

Phosphodiesterase inhibitors prevent the degradation of cGMP and cAMP. The cAMP and cGMP are activated by NO and are intermediaries in a pathway that leads to vasodilation via the activation of protein kinases and reduction in cytosolic calcium. Milrinone is an adenosine-3',5'-cAMP-selective phosphodiesterase enzyme inhibitor. When nebulized, it has been shown to lead to a relative reduction in PVR compared to SVR.¹²⁸ The inhalation of milrinone selectively dilated the pulmonary vasculature without systemic effects. When milrinone is combined with inhaled prostacyclin, there appears to be a potentiation and prolongation of the pulmonary vasodilatory effect.¹²⁹

Owing to the relatively higher expression of phosphodiesterase 5 in the pulmonary circulation relative to the systemic circulation, phosphodiesterase 5 inhibitors have a relative selective effect on PVR as opposed to SVR. In addition to their relatively selective pulmonary vasodilatory effects, their effects on smooth muscle proliferation and cellular apoptosis may be responsible for benefit of these agents when administered chronically in patients with idiopathic pulmonary arterial hypertension. A direct effect on the right ventricle has been postulated; however, the clinical relevance of this finding is uncertain.

Although the benefits of oral sildenafil and tadalafil in chronic pulmonary arterial hypertension have been evaluated in prospective controlled trials, most of the acute applications for these agents have been described in case reports or small cohort studies and as such have not been approved for these indications. In the acute setting, sildenafil has been demonstrated to enhance the effects of iNO and may also be useful in blunting the rebound in pulmonary pressures that occurs during weaning of iNO.¹³⁰ The benefits of sildenafil in acute pulmonary embolism, cardiac transplantation, and in patients with PHTN being considered for pulmonary thromboendarterectomy have also been described.¹³¹

Hypoxic Pulmonary Vasoconstriction

The IV anesthetic agents have no effect on hypoxic pulmonary vasoconstriction (HPV). All of the volatile anesthetics inhibit HPV in a dose-dependent fashion. Animal studies suggest that this inhibition is dependent on the agent: halothane > enflurane > isoflurane/desflurane/sevoflurane.¹³² The older agents were potent inhibitors of HPV, and this may have contributed to the high incidence of hypoxemia reported during OLV in the 1960s and 1970s (see earlier); many of these studies used 2 to 3 minimum alveolar concentration (MAC) doses of halothane during anesthesia.

In doses of less than or equal to 1 MAC, the modern volatile anesthetics (isoflurane, sevoflurane,¹³³ and desflurane¹³⁴) are weak, and equipotent, inhibitors of HPV. The inhibition of the HPV response by 1 MAC of a volatile agent such as isoflurane is approximately 20% of the total HPV response, and this could account for only a net 4% increase in total arteriovenous shunt during OLV, which is a difference too small to be detected in most clinical studies.¹³⁵ In addition, volatile anesthetics cause less inhibition of HPV when delivered to the active site of vasoconstriction via the pulmonary arterial blood than via the alveolus. This pattern is similar to the HPV stimulus characteristics of oxygen. During established OLV, the volatile agent only reaches the hypoxic lung pulmonary capillaries via the mixed venous blood. No clinical benefit in oxygenation during OLV has been shown for total IV anesthesia above that seen with 1 MAC of the modern volatile anesthetics.¹³⁶ Nitrous oxide inhibits HPV. Nitrous oxide is usually avoided during thoracic anesthesia.

The HPV is decreased by systemic vasodilators such as nitroglycerin and nitroprusside. In general, vasodilators can be expected to cause some deterioration in PaO_2 during anesthesia. Thoracic epidural sympathetic blockade probably has little or no direct effect on HPV, which is a localized chemical response in the lung.¹³⁷ However, thoracic epidural anesthesia can have an indirect effect on oxygenation if it is allowed to cause hypotension and a fall in CO, thus decreasing mixed venous oxygen saturation.

Intrinsic Pharmacologic Effects of the Lungs

The lungs receive essentially the entire CO and the surface area of their vascular bed is enormous (70-100 m^2). The lungs contain nearly half of the body's endothelium and have an extraordinarily high perfusion of 14 mL/min/g tissue (as opposed to the next highest renal perfusion of 4 mL/min/g tissue). Thus, there is ample blood-endothelial interface for surface enzyme activity as well as uptake and secretion.¹³⁸ The largest population of cells involved in pulmonary metabolism of blood-borne substances is, as might be expected, the pulmonary endothelium. Consistent with high metabolic activity, endothelial cells typically have both extensive cytoplasmic vesicles and prominent caveolae. The caveolae are tiny membrane invaginations and near-membrane vesicles similar to those found elsewhere in the body, measuring 50 to 100 nm, associated with caveolin proteins, and derived from lipid rafts within the membrane. The predominant activities of these caveolae, thought to include endocytosis and signal transduction, have not been fully delineated and may be pleiotropic.¹³⁹ The endothelial cells structurally have large luminal projections and invaginations, providing an even greater interface area at the microscopic level.

Metabolism by the endothelial cell occurs either on the surface of the cell via enzymes associated with the membrane ("ectoenzymes") or by cytosolic processing after substances are taken up by the cell. Some surface enzymes are distributed along the luminal membrane, whereas others are associated exclusively with the caveolae. **Figure 25.4** schematically depicts these processes with example substances and pathways. Metabolism may be further divided into exogenous versus endogenous substances as well as deactivated versus activated products. The terminology of pulmonary metabolism can be confusing and sometimes

inconsistent. In general, “pulmonary uptake” (or “extraction”) is simply used to describe transfer from blood to lung. It does not indicate whether the substance of interest is subsequently metabolized or returned back into the blood (with or without alteration). “First-pass” uptake is used to describe the amount of substance removed from the blood on the first cycle through the lungs. “Extraction” is also sometimes misused synonymously with first-pass uptake. “Clearance” may be used to describe a substance undergoing actual elimination, either in terms similar to renal clearance as volume of blood from which the substance would be completely removed (milliliters per minute or milliliters per kilogram per minute), or as a comparison of pulmonary arterial concentration versus systemic arterial concentration.

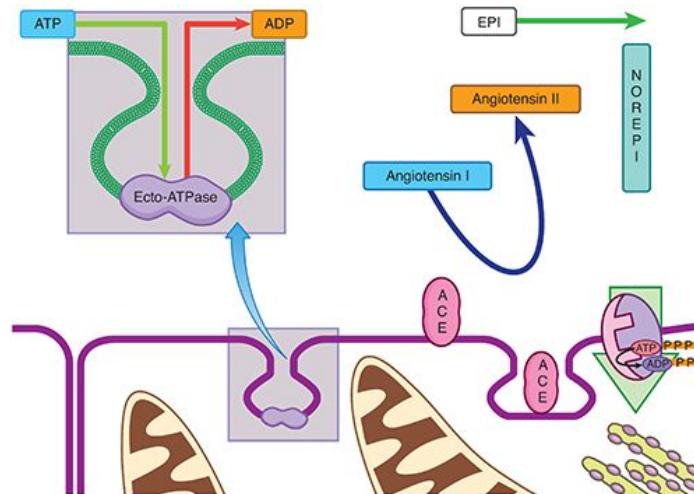


FIGURE 25.4 Schematic examples of pulmonary endothelial metabolism. Surface enzymes may be restricted to the caveolae (ecto-adenosine triphosphatase [ecto-ATPase] in the inset earlier is an example) or present on both the luminal surface and caveola (eg, angiotensin-converting enzyme [ACE]). Another characteristic of pulmonary endothelium is selective uptake, here exemplified by the adenosine triphosphate (ATP)-dependent uptake of norepinephrine (NOREPI), while epinephrine (EPI) is not taken up. Abbreviation: ADP, adenosine diphosphate. Reprinted by permission from Springer: Kleiman AM, Littlewood KE. *Nonrespiratory functions of the lungs*. In: Slinger P, ed. *Principles and Practice of Anesthesia for Thoracic Surgery*. 2nd ed. Cham, Switzerland: Springer; 2019:131-149. Figure 7.1. Copyright © 2019 Springer Nature Switzerland AG.

The lung has a pronounced impact on the blood concentration of substances even when it does not ultimately break them down or secrete them. This is because of simple uptake and retention of substances, often followed by release back into the blood. This “capacitor effect”¹⁴⁰ of the lungs in which any rapid rise or fall in concentration is attenuated is revisited in the following discussion regarding local anesthetic toxicity.

Exogenous Substances

Drugs

The cytochrome P450 monooxygenase enzyme systems are the most studied metabolic pathways for medications. The lungs have been found to have substantial concentrations of P450 isoenzymes, particularly within type II pneumocytes, Clara cells, and endothelial cells. Although P450 and other enzyme systems have long been known to exist in the human lung, the actual activity of lung enzymes ranges from negligible to 33% of that of the liver.¹⁴¹

Opioids

Fentanyl has been shown to have a markedly variable first-pass uptake up to 90% in humans. The same investigators found that significant amounts of fentanyl then returned from the lungs into the blood with a biphasic pattern, equilibrating after about a minute in the fast phase and nearly 25 minutes for the slow phase.

The uptake of fentanyl is higher than expected even for this basic and lipophilic drug. Active uptake of fentanyl has been demonstrated in human lung endothelial cells. Sufentanil demonstrates uptake that is a little more than half that of fentanyl. Morphine has a much lower uptake of about 10%.^{[142](#)}

Local Anesthetics

For lidocaine, there is a first-pass uptake of approximately 50% with significant retention at 10 minutes.^{[143](#)} The uptake of lidocaine has also been examined in a variety of physiologic circumstances. Under extremes of metabolic acidosis and alkalosis, lidocaine demonstrates increased uptake with higher blood pH. It is postulated that this finding is the consequence of increased drug lipophilicity because, in a less acidic environment, more of the drug is in its nonionized form. Bupivacaine has been investigated less extensively than lidocaine and with less consistent results. In most animal species, peak extraction has been reported as high with variable first-pass retention. In humans, however, the effective first-pass extraction appears to be lower when studied by epidural dosing.^{[144](#)}

Two areas of interest in the practice of clinical anesthesia are intimately linked with the pulmonary uptake of local anesthetics. The first is the relative safety of levobupivacaine and ropivacaine in comparison to bupivacaine. These drugs have, in fact, been the subject of several investigations. Early animal studies suggested decreased toxicity of these newer preparations. However, a review of the pharmacodynamics and pharmacokinetics of local anesthetics^{[145](#)} describes the challenges of comparing toxicities in clinical practice. A second area of interest is the treatment of local anesthetic toxicity with lipid emulsion. The issue of pulmonary uptake and delayed release of local anesthetics must be considered in the treatment of suspected local anesthetic toxicity with emulsified lipid.^{[146](#)}

Hypnotics

Thiopental has been found to have nearly 15% first-pass uptake in humans^{[147](#)} with little or no metabolism. The pulmonary uptake of ketamine was found to be slightly less than 10% without subsequent metabolism.^{[148](#)} For propofol, most work shows about 30% first-pass uptake and negligible metabolism of propofol by the lungs.^{[149](#)}

Endogenous Substances

Angiotensin-Converting Enzyme

The lung plays a critical role in the renin-angiotensin system because of the pulmonary endothelium's high concentration of angiotensin-converting enzyme (ACE). When the kidney responds to changes in physiologic parameters such as vascular volume, blood pressure, and adrenergic stimulation by the cleaving of prerenin, the resultant renin catalyzes the formation of angiotensin I from angiotensinogen. It is ACE that then converts angiotensin I to the critically important vasoconstrictor, angiotensin II. Although ACE can be found on vascular endothelium throughout the body as well as in the plasma, the pulmonary endothelium has an abundance of ACE as a surface or an ectoenzyme on the vascular membrane (**Figure 25.5**).^{[150](#)} The newly formed angiotensin II is not taken up or further metabolized by the endothelial cell but rather immediately returns to the blood. Clinically, ACE inhibitors have been useful drugs in the management of systemic hypertension.^{[151](#)}

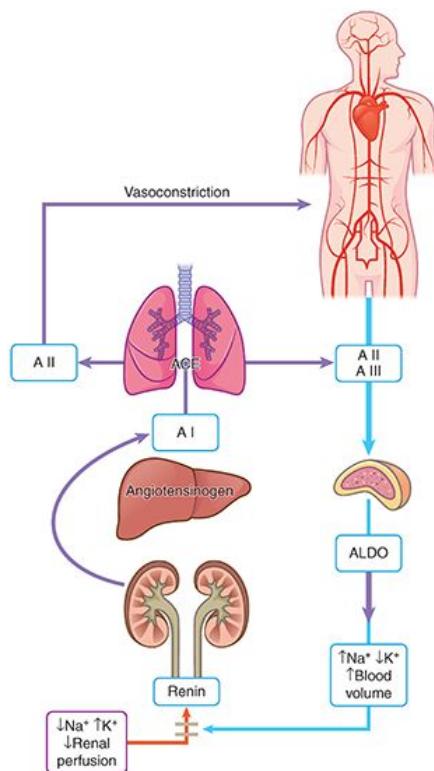


FIGURE 25.5 An example of the lung's central role in the body's endocrine processes, in this case the renin-angiotensin-aldosterone axis. In response to sodium (Na), potassium (K), and renal perfusion changes, renin is secreted by the kidneys. Renin cleaves angiotensinogen (renin substrate) from the liver to form angiotensin I (A I). The lung then converts A I to A II through the action predominately of endothelium-associated angiotensin-converting enzyme (ACE). The A II causes vasoconstriction and is involved in stimulation of aldosterone (ALDO) secretion by the adrenal gland, resulting in retention of Na and volume by the kidney. *Reprinted by permission from Springer: Kleiman AM, Littlewood KE. Nonrespiratory functions of the lungs. In: Slinger P, ed. Principles and Practice of Anesthesia for Thoracic Surgery. 2nd ed. Cham, Switzerland: Springer; 2019:131-149. Figure 7.2. Copyright © 2019 Springer Nature Switzerland AG.*

Bradykinin is a nine-amino acid peptide produced in multiple sites throughout the body from kininogen through the action of plasma kallikrein. It is in turn metabolized by several peptidases. Bradykinin is degraded by ACE and more than 90% of bradykinin is eliminated on first pass through the lungs.¹⁵² Bradykinin's effects are wide ranging, including antithrombotic and profibrinolytic activity in the coagulation system, as well as modulation of NO and prostacyclin release. Specific to the lung, bradykinin has vasodilating effects on normal pulmonary vessels but is vasoconstrictive when the pulmonary endothelium is destroyed in animal models.¹⁵³ Bradykinin is a bronchoconstrictor.¹⁵⁴ Some side effects of ACE inhibitors, such as angioedema and cough, and some of the beneficial impact, such as decreased myocardial infarctions and improved renal function, involve modification of bradykinin metabolism.

Biogenic Amines

Histamine; serotonin (5-hydroxytryptamine or 5-HT); and the three naturally occurring catecholamines, dopamine, norepinephrine, and epinephrine, comprise the group commonly termed *biogenic amines*. 5-HT is produced predominately by the gastrointestinal tract's chromaffin cells. Ingested tryptophan undergoes a two-step conversion first by tryptophan-5-hydroxylase and then by L-amino acid decarboxylase to serotonin. Mast cells and neuroendocrine cells in the lung are also capable of producing serotonin by uptake of tryptophan along the same enzymatic pathway. Once released from the gastrointestinal tract, there is avid uptake of 5-HT, particularly by nerve endings and platelets. These cells do not metabolize 5-HT to any great extent. The

remainder of 5-HT is extracted by the lung and, to a lesser degree, the liver. In the case of these organs, the 5-HT is metabolized to 5-hydroxyindoleacetic acid by cytosolic monoamine oxidase (MAO) and aldehyde dehydrogenase. 5-Hydroxyindoleacetic acid is a useful marker of carcinoid syndrome with increased histamine turnover. The MAO inhibitors block the cytosolic metabolism of 5-HT but not its uptake, whereas several drugs, including volatile anesthetic agents, block uptake but not intracellular metabolism.¹⁵⁵

Because it is not lipophilic, the pulmonary uptake of 5-HT is an active process, predominately via endothelial cells and with some variability between species. The pulmonary uptake of 5-HT by the lung is typically reported to be 90% or greater, meaning that little 5-HT reaches the systemic vasculature under normal circumstances. This model of production and uptake of 5-HT plays a pivotal role in several pathologic processes relevant to clinical anesthesiology. In carcinoid syndrome, the right heart receives a high concentration of 5-HT before being extracted and metabolized by the pulmonary circulation. This is thought to be the reason that the right heart shows the greatest myocardial and valvular injury in this syndrome.¹⁵⁶ The valvular injury of substances related to 5-HT such as methysergide and ergotamine, and those that increase 5-HT such as fenfluramine, and the recreational drug “ecstasy” (3,4-methylenedioxymethamphetamine), known to activate 5-HT receptors, are all similar to carcinoid cardiac disease. When an intracardiac right-to-left shunt is present in the carcinoid patient with a partial bypass of the pulmonary circulation, the left heart demonstrates valvular injury similar to that of the right heart.¹⁵⁷

Pulmonary embolism presents another clinical situation pertinent to 5-HT activity. The mass effect of embolism does not, in itself, account for the typical cardiopulmonary consequences. The platelet aggregation and activation associated with acute pulmonary embolism results in degranulation with the release of 5-HT, well known to be a potent vasoconstrictor and to increase bronchial smooth muscle tone. This release of 5-HT and, perhaps, decreased local uptake of 5-HT are postulated to cause local and regional vascular changes. Other actions of elevated 5-HT, such as promotion of further platelet aggregation and inhibition of the vasodilating prostacyclin likely also play a role in the full response to pulmonary embolism.¹⁵⁸ Histamine, in contrast to 5-HT, has almost no uptake in the pulmonary circulation.

Just as the lung has the enzymes to metabolize both histamine and serotonin but the ability to take up only serotonin, its uptake of catecholamines also demonstrates marked selectivity. Norepinephrine demonstrates a 35% to 50% first-pass uptake with subsequent metabolism by catechol-O-methyltransferase, MAO, aldehyde reductase, and aldehyde dehydrogenase.¹⁵⁹ However, dopamine, isoproterenol, and epinephrine have essentially no uptake.

Arachidonic Acid Metabolites

Extensive production and metabolism of arachidonic acid derivatives occurs in the lung. The term *eicosanoids* refers to the 20-carbon carboxylic acids derived from the metabolism of the lipid membrane component icosatetraenoic acid, more commonly known as arachidonic acid. The action of phospholipase A₂ converts the esterified form, as found in the membrane, and releases arachidonic acid from structural glycerol. Once free, arachidonic acid may follow three main metabolic pathways in the lung: the lipoxygenase pathway produces leukotrienes, lipoxins, and some of the hydroxyeicosatetraenoic acids (HETEs); the cyclooxygenase (COX) pathway produces prostaglandins, thromboxane, and prostacyclin; and the cytochrome P450 monooxygenase system produces cis-epoxyeicosatrienoic acids and HETEs that are different than the products of the lipoxygenase pathway.

The leukotrienes promote inflammatory responses in the lung. They are responsible for bronchoconstriction and increased pulmonary vascular permeability, are chemotactic and chemokinetic for neutrophils, and facilitate eosinophil degranulation.¹⁶⁰ They are produced by activated inflammatory cells within the lung as well as those arriving in response to inflammation. The lipoxins have become identified as critical factors in the resolution of inflammation throughout the body.¹⁶¹ They inhibit eosinophil and neutrophil chemotaxis and adhesion as well as natural killer cell activation. They are endothelium-dependent vasodilators of both pulmonary and systemic vasculature.

The COX catalyzes the cyclization and oxygenation of arachidonic acid, producing prostaglandin G2, which is converted to prostaglandin H2. There are subtypes of the COX enzyme, most notably COX-1 and

COX-2. There has been great interest in COX-2 since its discovery in the 1990s because its inhibition was hoped to be more specific in controlling pain and inflammation without injury to the gastroduodenal mucosa. Although effective, the emergence of a small but real increase in cardiovascular risk of COX-2 inhibitors has tempered their use.¹⁶² Complicating this issue further, many of the nonspecific COX inhibitors such as acetaminophen, salicylates, and the nonsteroidal antiinflammatory agents ibuprofen and naproxen show only slightly less COX-2 avidity than some of the newer COX-2-specific inhibitors. Following the production of prostaglandin H₂, the metabolic pathway divides into branches producing the various bioactive prostanoids; the enzymes of particular interest here are prostaglandin D synthase, prostaglandin E synthase, prostacyclin synthase, and thromboxane synthase. The final products of these pathways typically have opposed or balancing effects locally and regionally. Prostaglandin E₂ and prostacyclin are bronchodilators, for example, whereas prostaglandin F_{2α} (PGF_{2α}), prostaglandin D₂, and thromboxane A₂ cause bronchoconstriction. Similarly, prostaglandin D₂, prostaglandin E₂, PGF_{2α}, and thromboxane A₂ are potent vasoconstrictors, whereas prostaglandin E₁ and PGF₂ are vasodilators.

The cytochrome P450 monooxygenase system provides three pathways of arachidonic acid metabolism, which result in epoxyeicosatetraenoic acids (EETs), HETEs, or dihydroxyeicosatetraenoic acids. The HETEs and EETs have been shown experimentally to affect pulmonary vascular and bronchomotor tone. The 20-HETE and 5-, 6-, 11-, and 12-EETs all have relaxing effects on both the lung vasculature and airways. They are further known to have general antiinflammatory effects, to modulate reperfusion injury, and to inhibit platelet aggregation. Within the lung, 15-HETE and 20-HETE may both modify hypoxic vasoconstriction.¹⁶³

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Acid–Base Disorders

Peter Slinger

The management of acid–base disorders requires establishing the cause(s) of the disorder and then treating the underlying physiologic derangement. The treatment of acid–base disturbances is complex for a variety of reasons including the fact that the laboratory information on which we make decisions is rarely complete. This is because we often do not have access to all the data, which influence a patient’s acid–base status (eg, serum phosphate, sulfate). The acid–base disturbance is often evolving rapidly (eg, ischemia, shock), and there may be a delay getting laboratory results. The algorithms that have been designed to help us understand acid–base therapy are based on steady-state conditions and the terminology that we use to describe acid–base chemistry is not intuitive ([Table 26.1](#)). However, using only blood gas and common serum biochemistry data, we can manage the majority of clinical acid–base disorders.

The central focus of treating acid–base disturbances is understanding the biochemistry of the hydrogen ion. Hydrogen ion concentrations in the various body fluid compartments are precisely regulated in the face of enormous variations in local production and clearance. Deviations in hydrogen ion concentrations from the normal range can cause marked alterations in protein structure and function, enzyme activity, and cellular function. Although hydrogen ions are continuously produced in the hydrolysis of adenosine triphosphate, the largest contribution of metabolic acids arises from the oxidation of carbohydrates, principally glucose, to produce carbon dioxide (volatile acid, approximately 24,000 mEq per day). By comparison, the average net production of nonvolatile metabolic acid, such as lactate, is relatively small (approximately 60 mEq per day).

The hydrogen ion concentration is regulated to maintain the arterial blood pH between 7.35 and 7.45. However, expression of the hydrogen ion concentration as pH masks large variations in hydrogen ion concentration despite small changes in pH. For example, a pH range of 7.0 to 7.7 is associated with a fivefold change (100–20 nmol/L) in hydrogen ion concentration. The pH of venous blood and interstitial fluid is lower than that of arterial blood (approximately 7.35).

TABLE 26.1

Basic definitions

p: a mathematical notation for a concentration expressed as the –log to the base 10; useful to describe substances present in the plasma in very low concentrations

pH: the concentration of free hydrogen ions (H^+) in a solution. The pH of water is 7.0 at 25°C and 6.8 at 37°C. The normal pH of most body fluids is 7.4 (range, 7.35–7.45). This means that there are 40 nmol/L of H^+ in plasma (for comparison, there are 140 million nmol/L of Na^+ [140 mmol/L] in plasma).

pH_i: intracellular pH

Acid: a substance that increases the hydrogen ion concentration of a fluid (proton donor)

Alkali (or base): a substance that decreases the hydrogen ion concentration of a fluid (proton acceptor)

Buffer: a substance that reduces the change of pH in a solution when amounts of acid or base are added

K_a: the dissociation constant for a dissolved acid (HA), that is, the equilibrium ratio: $[H^+] [A^-] / [HA]$

pK_a: the –log of K_a for a given acid, for example, for carbonic acid (H_2CO_3), pK_a = 6.2. By convention, “strong” acids (eg, HCl) have a pK_a < –2 (more free H^+ at equilibrium) and “weak” acids (eg, H_2CO_3) have a pK_a –2 to +12 (this is confusing, but due to the negative logarithmic notation, a smaller number indicates a higher concentration of free H^+).

Anions: a negative ionized particle (eg, HCO_3^- , Cl^-), that is, an excess of electrons vs protons

Cations: a positively charged particle (eg, Na^+ , K^+), that is, an excess of protons vs electrons

Strong ions: the ions of substances that are completely dissociated in body fluids (eg, Na^+ , Cl^- , K^+ , SO_4^{2-} , Mg^{2+} , Ca^{2+})

Mole (mol): a fixed number [6.022×10^{23} (Avogadro number)] of elementary entities (atoms, molecules, ions, electrons, etc)

Molecular weight (MW) (actually, the “molecular mass”): the mass of 1 mole of a specific entity

Equivalent (Eq): the amount of a substance that will supply or react with 1 mole of H^+ ions (in acid–base reactions) or supply 1 mole of electrons (in oxidation–reduction reactions) mmol = mol/1,000, mEq = Eq/1,000. For singly charged particles (eg, Na^+), 1 mmol/L = 1 mEq/L; for doubly charged particles (eg, Mg^{2+}), 1 mmol/L = 2 mEq/L

Mole day: an informal annual holiday based on Avogadro number on October 23 (10/23) from 6:02 AM to 6:02 PM

Mechanisms for Regulation of Hydrogen Ion Concentration

Regulation of pH over a narrow range depends on (1) buffer systems, (2) ventilatory responses, and (3) renal responses. The buffer system mechanism is local and immediate but incomplete. Ventilatory responses are slower (minutes) and usually incomplete. Renal responses develop very slowly (hours) but can produce nearly complete pH correction.

Buffer Systems

Body fluids contain acid–base buffer systems that immediately combine with acid or alkali to prevent excessive changes in the hydrogen ion concentration. This ability to neutralize excess protons maintains the local pH near 7.4 in the face of continuous acid generation. The most important buffer systems are (1) bicarbonate and carbonic acid in plasma, interstitial and intracellular fluid, and bone; (2) hemoglobin and other proteins in intracellular fluid; (3) plasma proteins; and (4) phosphates in intracellular and extracellular fluid and the kidney ([Figure 26.1](#)).

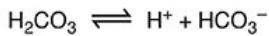
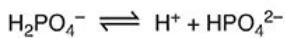
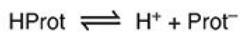
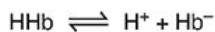


FIGURE 26.1 Buffering systems present in the body. Abbreviations: Hb, hemoglobin; Prot, protein.

Bicarbonate Buffering System

The bicarbonate buffering system consists of carbonic acid and sodium bicarbonate. Bicarbonate buffer is primarily a product of the approximately 200 mL of carbon dioxide produced per minute, of which considerably less than 1% dissolves to become carbonic acid. Carbonic acid is a weak acid because of its limited degree of dissociation (<5% at physiologic pH) into hydrogen and bicarbonate ions ([Figure 26.2](#)). Most carbonic acid in solution almost immediately dissociates into carbon dioxide and water, the net result being a very high concentration of dissolved carbon dioxide compared to the concentration of bicarbonate ions. This relationship is described mathematically by the Henderson-Hasselbalch equation, which can be used to calculate the pH of a solution if the concentration of bicarbonate ions and dissolved carbon dioxide is known ([Figure 26.3](#)).



FIGURE 26.2 Hydration of carbon dioxide results in carbonic acid (H_2CO_3), which can subsequently dissociate into bicarbonate and hydrogen ions.

$$\text{pH} = 6.10 + \log \frac{\text{HCO}_3^-}{\text{Paco}_2 (0.03)}$$

FIGURE 26.3 The Henderson-Hasselbalch equation can be used to calculate the pH of blood from the concentration of bicarbonate (HCO_3^-) and the Paco_2 .

The addition of a strong acid such as hydrochloric acid to the bicarbonate buffering system results in conversion of the strong acid to weak carbonic acid (Figure 26.4). Therefore, a strong acid lowers the pH of body fluids only slightly. The addition of a strong base, such as potassium hydroxide, to the bicarbonate buffering system results in the formation of a weak base and water. Buffers are most effective when they operate at a pH that is close to their pK_a (under these circumstances, the buffer system is approximately 50% dissociated). The bicarbonate buffering system is not a powerful buffer because its pK_a of 6.1 differs greatly from the normal pH of 7.4. Physiologically, buffers are most effective when their pK_a is equal to normal pH. However, the bicarbonate system is important because (1) bicarbonate is present in significant quantities in nearly all fluid compartments, (2) the concentration of its components is ultimately regulated by the lungs and kidneys, and (3) in severe acidosis the pH approaches the pK_a of the bicarbonate system thus increasing its efficiency.

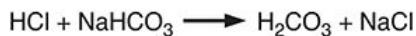


FIGURE 26.4 The addition of a strong acid (hydrochloric acid [HCl]) to the bicarbonate buffering system results in the formation of weak carbonic acid (H_2CO_3).

The bicarbonate buffer system accounts for >50% of the total buffering capacity of blood. Approximately one-third of the bicarbonate buffering capacity of blood occurs within erythrocytes. The electrical charge of bicarbonate ions limits their diffusion into cells other than erythrocytes.

Hemoglobin Buffering System

Hemoglobin is a particularly effective buffer because it is localized in quantity in erythrocytes; it has a pK_a of 6.8 and has a buffering capacity that varies with oxygenation. The imidazole ring of the amino acid histidine has a pK_a that is close to the physiologic pH. Thus, hemoglobin and other histidine-containing proteins are excellent physiologic buffers. Furthermore, deoxygenated hemoglobin is a weaker acid (better proton acceptor) than oxyhemoglobin. Thus, in the systemic capillaries, dissociation of oxyhemoglobin to deoxyhemoglobin facilitates the binding of hydrogen ions produced by the dissociation of carbonic acid. This situation is reversed in the pulmonary circulation where the conversion of deoxyhemoglobin to oxyhemoglobin facilitates the release of hydrogen ions.

Protein Buffering System

Like hemoglobin, other histidine-containing proteins are important intracellular buffers. Proteins are localized in high concentrations within the cell where it is estimated that approximately 75% of all the buffering of body fluids occurs, mostly by proteins. Of particular importance is the local buffering of hydrogen ions by proteins in the mitochondria. Although the relatively low concentration of plasma proteins limits their role as extracellular buffers, hypoproteinemia will further reduce buffering capacity, especially in the critically ill patient.

Phosphate Buffering System

The phosphate buffering system is important in most fluid compartments but is especially important in renal tubules, where phosphate is concentrated. Renal tubular fluid is more acidic than extracellular fluid, bringing the pH of renal tubular fluid closer to the pK_a (6.8) of the phosphate buffering system. Phosphate is a very

important intracellular buffer because it is the most abundant intracellular anion. Furthermore, the relatively acidic pH of intracellular fluid is closer to the pK_a of the phosphate buffering system than is the pH of extracellular fluid.

Intracellular pH Regulation

Although blood pH is commonly measured clinically, it is the intracellular pH (pH_i) that is of functional importance. The routine measurement and manipulation of pH_i is not possible in current practice. Indeed, during hypothermic cardiopulmonary bypass and hibernation, the pH_i in heart and brain tissue appears to be highly regulated despite significant deviations in systemic pH. Cellular metabolism, transmembrane transport, membrane potential generation, cell growth and division, cytoskeletal structure, and contractile function are processes that are crucially dependent on pH_i (**Table 26.2**). Furthermore, the optimal function of several organelles, including lysosomes and mitochondria, require that their local pH is significantly different from the general pH_i . Thus, there are highly regulated mechanisms to maintain local pH_i , including intracellular buffer systems and membrane-bound proton transporters. Indeed, the pH_i (7.0) is higher than is predicted by the -90 mV transmembrane potential (pH 6.8). As in the extracellular compartment, intracellular protons are rapidly bound to weak acids and bases resulting in a low free proton concentration.

TABLE 26.2

Intracellular functions affected by local pH

Cellular metabolism
Cytoskeletal structure
Muscle contractility
Cell–cell coupling
Membrane conductance
Intracellular messengers
Cell activation, growth, and proliferation
Cell volume regulation
Intracellular membrane flow

Ventilatory Responses

Ventilation is quantitatively the most important mechanism of acid removal, given the enormous daily production of volatile acid compared to nonvolatile acid. Ventilatory responses cannot return pH to 7.4 when a metabolic abnormality is responsible for the acid–base disturbance. This reflects the fact that the intensity of the stimulus responsible for increases or decreases in alveolar ventilation will begin to diminish as pH returns toward 7.4. As a “buffer,” ventilatory responses are able to buffer up to twice the amount of acids or bases as all the chemical buffers combined. However, compensation for extreme metabolic acidosis imposes a significant respiratory burden. If the bicarbonate is reduced to 10 mmol/L, the carbon dioxide tension must be reduced to 15 mm Hg in order to normalize the pH. Most patients cannot hyperventilate to below 20 mm Hg. Further, it is likely that the insult causing severe metabolic acidosis will also adversely affect respiratory muscle function, thus compromising the respiratory response.

Renal Responses

The day-to-day renal contribution to acid–base regulation is directed toward the conservation of bicarbonate and the excretion of hydrogen ions. Plasma bicarbonate is freely filtered at the glomerulus. Almost all filtered bicarbonate must be reabsorbed from the glomerular filtrate to maintain the normal plasma bicarbonate concentration (25 mEq/L) and plasma pH. Most bicarbonate reabsorption occurs in the proximal convoluted tubule and is facilitated by the presence of carbonic anhydrase in the luminal fluid and is driven by the sodium-potassium-ATPase pump in the peritubular cell membrane. Active sodium ion extrusion from the

renal tubular cell into the peritubular circulation favors sodium diffusion from the tubular lumen into the tubular cell in exchange for hydrogen ions. Hydrogen in the renal tubular fluid then combines with filtered bicarbonate to form carbonic acid. Carbonic anhydrase facilitates the dissociation of carbonic acid into water and carbon dioxide that both enter the renal tubular cell. Carbon dioxide and water generate bicarbonate, which enters the peritubular circulation accompanied by sodium. The remaining hydrogen ions are secreted into the lumen in exchange for sodium (Figure 26.5). Inhibition of carbonic anhydrase by acetazolamide interferes with the reabsorption of bicarbonate ions from renal tubular fluid. As a result, excess bicarbonate ions are lost in the urine and the plasma bicarbonate concentration is decreased.

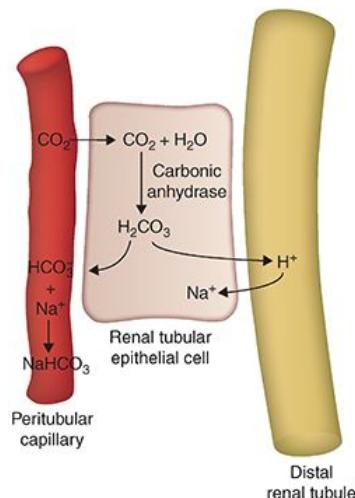


FIGURE 26.5 Schematic depiction of the renal tubular secretion of hydrogen ions, which are formed from the dissociation of carbonic acid in renal tubular epithelial cells.

Hydrogen ions are secreted into renal tubules by epithelial cells lining proximal renal tubules, distal renal tubules, and collecting ducts. At the same time, sodium ions are reabsorbed in exchange for the secreted hydrogen ions and combine with bicarbonate ions in the peritubular capillaries. This process is facilitated by aldosterone. As a result, the amount of sodium bicarbonate in the plasma is increased during the secretion of hydrogen ions into renal tubules. Active hydrogen ion transport is inhibited when the urinary pH drops below 4.0. Thus, hydrogen ions must combine with ammonia and phosphate buffers in the renal tubular lumen to prevent the pH from decreasing below this critical level. Ammonia is generated in the mitochondria of the proximal tubule. Ammonia combines with hydrogen ions to form ammonium, which is excreted in the urine in combination with chloride ions as the weak acid ammonium chloride (Figure 26.6). In renal insufficiency, the capacity to generate urinary ammonia is impaired, thus reducing hydrogen ion excretion.

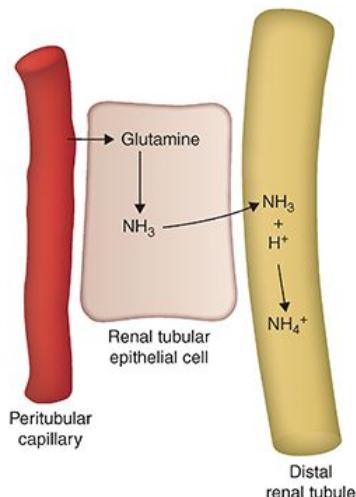


FIGURE 26.6 Ammonia formed in renal tubular epithelial cells combines with hydrogen ions in the renal tubules to form ammonium.

Renal responses that regulate hydrogen ion concentrations do so by acidification or alkalinization of the urine. In the presence of acidosis, the rate of hydrogen ion secretion exceeds the net loss of bicarbonate ion into the renal tubules. As a result, an excess of hydrogen ions is excreted into the urine. In the presence of alkalosis, the effect of the titration process in the renal tubules is to increase the number of bicarbonate ions filtered into the renal tubules relative to the secretion of hydrogen ions. Excess bicarbonate ions are excreted into the urine accompanied by cations, most often sodium.

Extracellular fluid is electroneutral such that the sum of the positive charges of all cations must equal the sum of negative charges of all anions. In the process of altering the plasma concentration of bicarbonate ions, it is mandatory to remove some other anion each time the concentration of bicarbonate ions is increased or to increase some other anion when the bicarbonate concentration is decreased. Typically, the anion that follows changes in the concentration of bicarbonate ions is chloride. As the most abundant extracellular anion, physiologic manipulation of chloride appears to be an important element of pH control. Conceptually, when bicarbonate ions are replaced by chloride ions, the pH will generally tend to decrease as a weak acid (carbonic acid) is replaced by a strong acid (hydrochloric acid).

The value of renal regulation of hydrogen ion concentration is not its rapidity but instead its ability to nearly completely neutralize any excess acid or alkali that enters the body fluids. Ordinarily, the kidneys can remove up to 500 mmol of acid or alkali each day. If greater quantities than this are generated, the kidneys are unable to maintain normal acid–base balance, and acidosis or alkalosis occurs. Even when the plasma pH is 7.4, a small amount of acid is still lost each minute. This reflects the daily production of 50 to 80 mmol of more acid than alkali. Indeed, the normal urine pH of approximately 6.4 is due to the presence of this excess acid in the urine.

Classification of Acid–Base Disturbances

Acid–base disturbances are categorized as respiratory or metabolic acidosis ($\text{pH} < 7.35$) or alkalosis ($\text{pH} > 7.45$) (Table 26.3).¹ An acid–base disturbance that results primarily from changes in alveolar ventilation is described as respiratory acidosis or alkalosis. An acid–base disturbance unrelated to changes in alveolar ventilation is designated as metabolic acidosis or alkalosis. Compensation describes the secondary renal or ventilatory responses that occur as a result of the primary acid–base disturbance.

	pH	PACO_2	Bicarbonate
Respiratory acidosis			

Acute	↓↓	↑↑↑	↑
Chronic	NC	↑↑↑	↑↑
Respiratory alkalosis			
Acute	↑↑	↓↓↓	↓
Chronic	NC	↓↓↓	↓↓
Metabolic acidosis			
Acute	↓↓↓	↓	↓↓↓
Chronic	↓	↓↓↓	↓↓↓
Metabolic alkalosis			
Acute	↑↑↑	↑	↑↑↑
Chronic	↑↑	↑↑	↑↑↑

Abbreviations: ↑, increase; ↓, decrease; NC, no change from normal.

The principal manifestation of severe respiratory or metabolic acidosis is depression of the central nervous system. For example, coma is a characteristic of severe diabetic acidosis or renal dysfunction leading to uremia. The principal manifestation of respiratory or metabolic alkalosis is increased excitability of the peripheral nervous system and central nervous system. As a result, there may be repetitive stimulation, causing skeletal muscles to undergo sustained contraction known as tetany. Tetany of respiratory muscles may interfere with adequate ventilation of the lungs. Central nervous system excitability may manifest as seizures.

Respiratory Acidosis

Any event (drug or disease) that decreases alveolar ventilation results in an increased concentration of dissolved carbon dioxide in the blood (increased PaCO_2), which in turn leads to formation of carbonic acid and hydrogen ions. By convention, carbonic acid resulting from dissolved carbon dioxide is considered a respiratory acid, and respiratory acidosis is present when the pH is <7.35 and PaCO_2 is >45 mm Hg. It is important to note that although an increase in dissolved carbon dioxide generates an equivalent increase in both the hydrogen ion and bicarbonate ion concentrations, the pH will fall. This is because the relative increase in hydrogen ions is significantly greater than the relative increase in bicarbonate ions because the plasma concentration of hydrogen ion is far lower than the concentration of bicarbonate. An increase in carbon dioxide sufficient to reduce the pH from 7.4 to 7.1 will essentially double the hydrogen ion concentration from 40 to 79 nmol/L, compared to an increase in the bicarbonate ion concentration only from 24.000000 to 24.000039 mmol/L.

Acidosis, respiratory or metabolic, often has profound effects on many drug and enzyme interactions in the body, which function optimally only within normal pH ranges. Of particular importance to the anesthesiologist is the clinical scenario of increasing respiratory acidosis due to inadequate reversal of muscle relaxants and the interaction between anticholinesterases and the enzyme acetylcholinesterase. The commonest method to reverse the muscle relaxant effects of nondepolarizing neuromuscular-blocking agents (NMBAs) is by administering an anticholinesterase, such as neostigmine. Anticholinesterases inhibit normal acetylcholinesterase, increasing the concentration of acetylcholine in the synaptic clefts of the neuromuscular junction and thus antagonizing the neuromuscular block. The concentration of NMBAs remains essentially unchanged at the time of reversal. If the reversal is inadequate due to an excess of NMBAs or due to the limited duration of action of the anticholinesterase (eg, 20-30 minutes for neostigmine), then inadequate alveolar minute ventilation can lead to progressive respiratory acidosis, which will potentiate the NMBAs and weaken the effects of the anticholinesterase. This clinical picture of increasing muscle weakness after a seemingly appropriately reversed neuromuscular block has been termed *recurarization*.² Although this was more of a clinical problem with the older longer acting NMBAs (eg, pancuronium), it can still occur with the newer shorter acting drugs (eg, rocuronium).

Respiratory Alkalosis

Respiratory alkalosis is present when increased alveolar ventilation removes sufficient carbon dioxide from the body to decrease the hydrogen ion concentration to the extent that pH becomes >7.45 . A physiologic cause of respiratory alkalosis is hyperventilation due to stimulation of chemoreceptors by a low PO_2 associated with ascent to altitude. Kidneys compensate with time for this loss of carbon dioxide by excreting bicarbonate ions in association with sodium and potassium ions. This renal compensation is evident in individuals residing at altitude who have a nearly normal pH despite a low Paco_2 . A frequent cause of acute respiratory alkalosis is iatrogenic hyperventilation of the lungs as during anesthesia. Tetany that accompanies alkalosis reflects hypocalcemia due to the greater affinity of plasma proteins for calcium ions in an alkaline, compared with an acidic, solution.

Metabolic Acidosis

The most common and most confusing acid–base disorder that clinicians are required to manage is metabolic acidosis. Any acid formed in the body other than carbonic acid from carbon dioxide is considered a metabolic acid, and its accumulation results in metabolic acidosis. Acidosis impairs myocardial contractility and the responses to endogenous or exogenous catecholamines.³ Hemodynamic deterioration is usually minimal (in the awake state) when the pH remains >7.2 due to compensatory increases in sympathetic nervous system activity. Of great clinical importance are the accentuated detrimental effects of metabolic acidosis in individuals with underlying left ventricular dysfunction or myocardial ischemia or in those in whom sympathetic nervous system activity may be impaired, as by drug-induced β -adrenergic blockade or general anesthesia. Respiratory acidosis may produce more rapid and profound myocardial dysfunction than does metabolic acidosis, reflecting the ability of carbon dioxide to freely diffuse across cell membranes and exacerbate intracellular acidosis.

Acute metabolic acidosis has been treated with intravenous administration of an exogenous buffer, usually sodium bicarbonate, in the hope that normalizing pH will attenuate the detrimental effects of acidosis. The effectiveness of the use of sodium bicarbonate to treat metabolic acidosis is debatable.⁴ Sodium bicarbonate administration increases the carbon dioxide load to the lungs, leading to further increases in arterial and intracellular PCO_2 if alveolar ventilation is not concomitantly increased. It is estimated that 1 mEq/kg sodium bicarbonate, given intravenously, produces approximately 180 mL of carbon dioxide and necessitates a transient doubling of alveolar ventilation to prevent hypercarbia. In the presence of increased dead space ventilation, even greater increases in alveolar ventilation are required for carbon dioxide elimination to equal production. Even if Paco_2 is maintained normal, it is possible that tissue pH_i and the risk of ventricular fibrillation will not be altered by administration of sodium bicarbonate during cardiopulmonary resuscitation. Also, the standard formulation of sodium bicarbonate, 8.4%, is hypertonic, and this will have a plasma-expanding effect that contributes to dilutional acidosis (see the following text). However, if alveolar ventilation can be increased to deal with the increased carbon dioxide load from administration of sodium bicarbonate (initial bolus dose 0.5–1 mEq/kg), then it can be useful as a temporizing measure to help restore hemodynamic stability in shock combined with severe metabolic acidosis.⁵

Lactic Acidosis

Under normal circumstances, lactate is produced at a rate of approximately 1 mmol/kg per hour. Normal clearance of lactate maintains its serum concentration between 0.5 and 1.0 mmol/L. Most lactate is cleared by the liver, where it undergoes oxidation, gluconeogenesis, and eventual conversion to bicarbonate. Lactate undergoes both passive diffusion and active transport into the liver via a monocarboxylate transporter. However, active transport becomes saturated at serum lactate concentrations that exceed 2.5 mmol/L. Severe reductions in hepatic blood flow, which occur during shock, will decrease hepatic lactate clearance. Lactic acid is a strong acid and therefore dissociates almost completely under physiologic conditions into the lactate anion and a hydrogen ion. Although lactate accumulation has classically been taught to occur mainly during anaerobic glycolysis, it is now clear that significant lactate generation occurs under normoxic conditions. Indeed, lactate is an important gluconeogenic precursor and is involved in cell-to-cell signaling. However, in

the critically ill patient, lactate production may increase while lactate clearance is impaired, and lactic acidosis may occur. Point-of-care testing allows almost instantaneous lactate determinations to be performed in the operating room and intensive care unit. A serum lactate >1.5 mmol/L upon admission is an independent predictor of mortality in critically ill patients. Furthermore, failure to decrease lactate concentration to ≤ 1.0 mmol/L 24 hours after admission is also associated with significant mortality.

The investigational drug dichloroacetate decreases lactate concentration in cardiogenic shock, burns, diabetic ketoacidosis, and malaria. Dichloroacetate activates the mitochondrial pyruvate dehydrogenase complex, thus accelerating the irreversible oxidation of lactate via pyruvate to acetyl coenzyme A, which then enters the Krebs cycle. The buffer tris(hydroxymethyl)aminomethane can be used to treat metabolic acidosis and does not generate carbon dioxide. It may be particularly useful, as an alternative to sodium bicarbonate, to treat metabolic acidosis in patients who are hypernatremic.⁶

Dilutional Acidosis

Because the pH of water at 37°C is 6.8, any increase in the free-water volume of the body will contribute to acidosis (eg, administration of 5% dextrose). Dilutional acidosis also occurs when the plasma pH is decreased by extracellular volume expansion with chloride-containing solutions such as normal saline. Clinically, a hyperchloremic metabolic acidosis may accompany large-volume infusion of isotonic saline.⁷ Normal saline is commonly thought of as being a “physiologic” solution because it has an osmolarity close to plasma and does not lyse red blood cells. However, it has a pH (5.7) that is more acidic than plasma and contains significantly more chloride (154 vs 100 mmol/L) and slightly more sodium (154 vs 140 mmol/L) (**Table 26.4**). Thus, infusion of a large volume of normal saline will increase plasma chloride concentration to a relatively greater degree than sodium concentration. Chloride can be thought of as a strong acid (hydrochloric acid-proton donor), just as sodium can be thought of as a strong base (sodium hydroxide-hydroxyl donor).⁸

TABLE 26.4

Electrolytes in plasma and commonly available crystalloid solutions

Solution	Na	Cl	K	Ca	Mg	Lactate	Acetate	Gluconate	pH	mOsm
Plasma	144	107	5	2	1.5				7.4	290
NS	154	154							5.5	308
RL	130	109	4	3		28			6.5	273
Plasma-Lyte	140	98	5		3		27	23 (mmol)	7.4	294
Ionolyte	137	110	4		1.5		34		7.4	287

Abbreviations: Ca, calcium; Cl, chloride; K, potassium; Mg, magnesium; mOsm, osmolarity; Na, sodium; NS, normal saline; RL, Ringer lactate.

Other Causes of Metabolic Acidosis

Renal failure prevents excretion of acids formed by normal metabolic processes, and metabolic acidosis occurs. Severe diarrhea and associated loss of sodium bicarbonate rapidly leads to metabolic acidosis, especially in the pediatric age group. Lack of insulin secretion (diabetes mellitus) or starvation impairs glucose utilization, forcing tissues to metabolize fat to meet energy needs. As a result, the plasma concentration of ketones such as acetoacetic acid may increase sufficiently to cause metabolic acidosis.

Differential Diagnosis of Metabolic Acidosis

Several different methods have been developed over the past 60 years to help clinicians in the differential diagnosis and treatment of acid-base disturbances, particularly relating to metabolic acidosis. All of these methods have their strengths and their weaknesses because they are based on theoretical stable states. In clinical practice, these methods have been made less relevant by the ability to get rapid laboratory or point-of-care results for several plasma values such as lactate.

Base Excess

The concept of base excess (BE) and its converse base deficit were developed in the 1940s. This is defined as the amount of strong acid or base to return the plasma pH to 7.4 assuming PaCO_2 40 mm Hg and normothermia. The BE is calculated (not measured) by modern blood gas analyzers from an algorithm based on measured bicarbonate and pH. In isolated acute respiratory acidosis or alkalosis, the BE should not change (normal value = 0). The BE remains useful to alert the clinician to the presence of a concurrent metabolic acidosis ($\text{BE} < 0$) in the presence of a respiratory acidosis ($\text{pH} < 7.35$, $\text{PaCO}_2 > 45$ mm Hg) or to the presence of an underlying metabolic alkalosis ($\text{BE} > 0$). Mixed respiratory and metabolic acidosis is a common clinical problem. Also, it alerts the physician to the severity of the metabolic derangement, which can then be used as a guide to the initial therapy. The weakness of the BE measurement is that it does not distinguish among the possible causes of metabolic acidosis.

Anion Gap

Calculation of the anion gap may assist in the evaluation of acid–base disorders. The anion gap is a derived value based on the principle of electrochemical neutrality such that the sum of the positive (cationic) charges in a solution must equal the sum of the negative (anionic) charges. The major extracellular anions are chloride and bicarbonate. Other significant anions include proteins, phosphate, sulfate, and organic acids (including lactate). The latter are less commonly measured in routine practice and are referred to as *unmeasured anions*. The predominant extracellular cation is sodium. Although potassium is now routinely measured, its inclusion in the anion gap calculation is inconsistent and varies from institution to institution. Potassium is often grouped with the other “unmeasured cations,” calcium and magnesium. Under normal circumstances, the concentration of the predominant cation (sodium) exceeds that of the combined predominant anions (chloride and bicarbonate) [$\text{anion gap} = \text{Na}^+ - (\text{HCO}_3^- + \text{Cl}^-)$] by 9 to 13 mEq/L. For electroneutrality to occur, the concentration of the combined unmeasured anions must therefore exceed that of the unmeasured cations by the same amount. The term *anion gap* refers solely to the difference in concentration between the traditionally measured anions and cations. The anion gap does not imply a true discrepancy between the total positive and negative charges in physiologic solution where the total anion charge must equal the total cation charge.

Metabolic acidosis is most often associated with an increase in the anion gap (**Table 26.5**). An increase in the concentration of unmeasured anions (or a decrease in the concentration of unmeasured cations) will increase the anion gap. Lactic acidosis, ketoacidosis, and renal failure increase the concentration of unmeasured endogenous anions. Exogenous anions will also increase the concentration of unmeasured anions (salicylate toxicity, ethylene glycol, and methanol ingestion). Hyperchloremic acidosis and renal tubular acidosis (bicarbonate loss) will have a normal anion gap. The weaknesses of the anion gap concept include that it does not differentiate between the causes of increased anion gap metabolic acidosis; it does not correct for pH changes due to free-water volume increase or decreases; and it does not correct for changes in serum albumin and phosphate, which have an effect on acid–base balance.

TABLE 26.5

Causes of metabolic acidosis

Increased anion gap	Normal anion gap
<ul style="list-style-type: none">• Lactic acidosis• Ketoacidosis• Chronic renal failure (accumulation of sulfates, phosphates, urea)• Intoxication: organic acids (salicylates, ethanol, methanol, formaldehyde, ethylene glycol, paraldehyde), INH, sulfates, metformin• Massive rhabdomyolysis	<ul style="list-style-type: none">• Hyperchloremic acidosis (excess saline administration)• Diarrhea (long-standing bicarbonate loss)• Pancreatic fistula• Renal tubular acidosis• Intoxication: ammonium chloride, acetazolamide,

Abbreviation: INH, isoniazid.

Strong Ion Gap

The strong ion gap (SIG) method is also based on the concept of electroneutrality of plasma.⁹ The SIG compares the excess measured serum concentrations of strong cations (Na^+ , K^+ , Mg^{2+} , Ca^{2+}) to the calculated total of measurable anions (Cl^- , HCO_3^- , albumin, phosphate); the normal gap is 6 to 10 mEq/L. The SIG can be corrected for changes in plasma free-water volume and may be more useful in combined causes of metabolic acidosis, which are common in clinical practice. Measurement of the plasma lactic acid concentration and calculation of the anion gap from sodium, chloride, and bicarbonate permits differentiation of dilutional acidosis from acidosis due to tissue hypoperfusion.

Simplified Approach to Metabolic Acidosis of Uncertain Etiology

When the cause of a metabolic acidosis is unclear, measure the serum lactate, blood urea nitrogen, creatinine, and glucose. If this does not identify the etiology of the acidosis, then send serum for toxicology to measure salicylates, methanol, ethylene glycol, etc.

Metabolic Alkalosis

Metabolic alkalosis is commonly iatrogenic. Causes include vomiting with excess loss of hydrochloric acid, nasogastric suction, chronic administration of diuretics, hypoalbuminemia, and excess secretion of aldosterone. Excess administration of sodium bicarbonate may be an iatrogenic cause of metabolic alkalosis. A loss of free water (pH 6.8) will cause a volume-contraction alkalosis. Treatment involves treating the underlying cause.

Compensation for Acid–Base Disturbances

Respiratory acidosis is compensated for within 6 to 12 hours by increased renal secretion of hydrogen ions, with a resulting increase in the plasma bicarbonate concentration. After a few days, the pH will be normal despite persistence of an increased PaCO_2 . Sudden correction of chronic respiratory acidosis, by iatrogenic hyperventilation, may result in acute metabolic alkalosis because increased plasma bicarbonate is not promptly eliminated by the kidneys.

Respiratory alkalosis is compensated for by decreased reabsorption of bicarbonate ions from renal tubules. As a result, more bicarbonate ions are excreted in the urine, which decreases the plasma concentration of bicarbonate and returns the pH toward normal despite persistence of a decreased PaCO_2 .

Metabolic acidosis stimulates alveolar ventilation, which causes rapid removal of carbon dioxide from the body and decreases the hydrogen ion concentration toward normal. This respiratory compensation for metabolic acidosis, however, is only partial because pH remains somewhat below normal.

Metabolic alkalosis diminishes alveolar ventilation, which in turn causes accumulation of carbon dioxide and a subsequent increase in hydrogen ion concentration. As with metabolic acidosis, the respiratory compensation for metabolic alkalosis is only partial. Renal compensation for metabolic alkalosis is increased by reabsorption of hydrogen ions. This metabolic compensation is limited by the availability of sodium, potassium, and chloride ions. During prolonged vomiting, there may be excessive loss of chloride ions along with sodium and potassium. When this occurs, the kidneys preferentially conserve sodium and potassium ions and the urine becomes paradoxically acidic. Indeed, the presence of paradoxical aciduria indicates electrolyte depletion.

Effects of Temperature on Acid–Base Status

Temperature changes have several effects on blood and tissue pH and PCO_2 . As blood is cooled, carbon dioxide becomes more soluble. Therefore, for a given carbon dioxide content, the partial pressure will decrease as the temperature falls. The magnitude of this change is approximately 4.5% per degree Celsius and

will tend to increase the pH. The blood pH is further increased as the dissociation of water into protons and hydroxyl ions decreases with cooling, thus decreasing hydrogen ion concentration. In addition, proton buffering by hemoglobin α -imidazole groups is enhanced by hypothermia. The sum of these effects is an increase of 0.015 pH units per degree Celsius decrease in temperature. These changes are probably insignificant within the physiologic temperature range but are important when interpreting blood gas and acid–base data during induced cooling during cardiopulmonary bypass. If the blood temperature is decreased by 10°C to 27°C, the pH will increase to 7.6. Two alternate blood gas management strategies, “ α -stat” and “pH-stat,” are utilized during hypothermia in the operating room ([Table 26.6](#)).

TABLE 26.6

α -Stat versus pH-stat management during hypothermia

	α-Stat	pH-Stat
Carbon dioxide added to oxygenator	No	Yes
Enzyme function	Near normal	Decreased
Cerebral blood flow	Normal	Increased
Blood gas temperature correction required	No	Yes
Hb–O₂ dissociation curve	Marked left shift	Less marked left shift

Abbreviations: Hb, hemoglobin; O₂, oxygen.

pH-Stat Management

During hypothermic conditions, blood pH is increased and PCO₂ is decreased. The pH-stat strategy seeks to return the pH and PCO₂ of hypothermic blood to normal. During hypothermic cardiopulmonary bypass, this strategy usually involves the addition of carbon dioxide via the oxygenator. A purported advantage of this strategy is that cerebral blood flow will be increased because carbon dioxide is a potent cerebral vasodilator. However, delivery of microemboli to the brain may also be increased. Temperature correction of blood gas samples is required to interpret the values obtained from a hypothermic patient but measured at 37°C. The pH-stat strategy is used more often in surgery for pediatric congenital heart disease, especially during cooling and deep hypothermic circulatory arrest.¹⁰ Under these circumstances, enhanced cerebral perfusion that facilitates brain cooling is thought to be desirable. Cerebral injury secondary to global hypoperfusion is thought to be a greater threat than delivery of microemboli in this patient population. Hypothermia, hypocarbia (via the Bohr effect), and alkalosis, all shift the oxyhemoglobin dissociation curve to the left and impair tissue oxygen delivery. The addition of carbon dioxide during pH-stat management will counter these effects and facilitate oxygen unloading from hemoglobin.

α -Stat Management

The α -stat strategy seeks to replicate the alkalinization of blood that occurs during cooling in poikilothermic mammals (eg, naked mole rat). This strategy seeks to optimize enzyme function during hypothermia. The α of α -stat refers to the charged portion of the histidine imidazole residue. The objective is to maintain biologic neutrality by preserving the α -imidazole and protein charge state, the OH[−]/H⁺ ratio, and therefore enzyme function, even though the pH will increase. This strategy is most often used during adult cardiopulmonary bypass and does not generally encourage the delivery of microemboli to the brain because supplemental carbon dioxide is not generally administered. This strategy does not require temperature correction of blood gas results.

There are examples of both strategies in nature. Homeotherms (eg, humans) have homeostatic mechanisms for maintaining the temperature of the internal environment within very narrow limits. Homeotherms and hibernating animals hypoventilate in order to maintain blood pH at 7.4 as their body temperature decreases (pH-stat). The pH_i is low in most tissues under these circumstances and suppresses metabolism and conserves energy stores in nonfunctioning tissues. However, the brain and heart of these

animals employ α -stat strategies to maintain pH_i at α -stat values and to maintain near-normal function. Poikilotherms (eg, snakes) have not developed mechanisms for regulating the temperature of their internal environment that changes with that of the external environment. Poikilotherms use the α -stat strategy and allow their blood pH to increase and PCO_2 to decrease with cooling in order to preserve cellular and enzyme function over wide temperature ranges.

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PART V Blood and Hemostasis

Physiology of Blood and Hemostasis

Jerrold H. Levy

Understanding the physiology of blood and its interactions for hemostasis is a critical aspect of managing perioperative bleeding. With the increasing use of anticoagulation therapies for cardiovascular diseases, patients also present with multiple underlying acquired coagulation abnormalities. Further, in an acutely bleeding and hemorrhagic patient, additional coagulation changes occur that are covered in the chapter on physiology and management of massive transfusion. Understanding the physiology of coagulation and blood interactions is important in determining the preoperative bleeding risk of patients and in managing hemostatic therapy perioperatively.

At the center of hemostasis is the ability to generate thrombin, a serine protease. Thrombin plays pivotal roles in the activation of additional coagulation factors as shown in [Figures 27.1](#) and [27.2](#).¹ Most coagulation factors circulate in the body as inactive enzymatic precursors that are called **zymogens**.¹ However, there are multiple critical steps in clot formation that involve additional cofactors, humoral proteins, cellular components, and cell surface receptors. Following tissue injury, thrombin is generated in a highly regulated way that keeps the effects of this activation local to the site of injury and prevents uncontrolled systemic thrombosis. In surgical patients, multiple perturbations occur, and the hemostatic and inflammatory systems are closely related and have significant cross talk. Managing perioperative hemostasis also requires consideration of the postoperative hypercoagulability that may follow, and important advances have been made as new pharmacologic strategies are available and used to treat both procoagulation states and cardiovascular disease. This chapter reviews the physiology of hemostasis, clot formation, and thrombin generation.

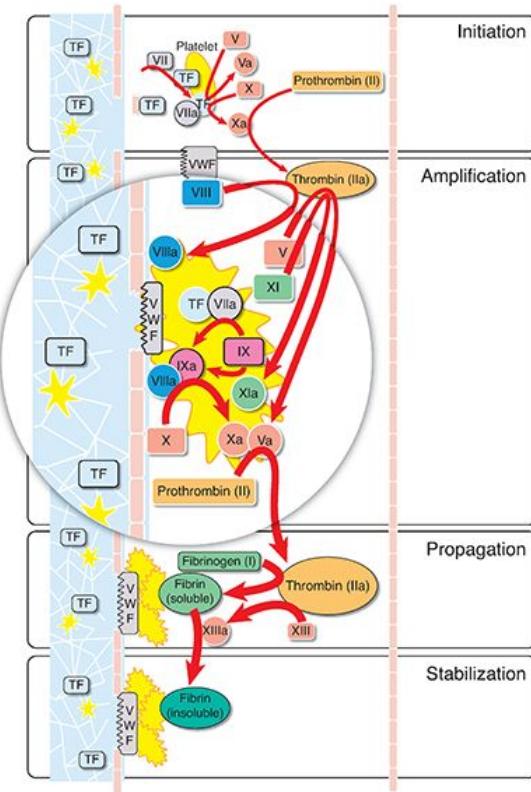


FIGURE 27.1 Initiation, amplification, propagation, and stabilization of hemostasis and clot formation. This describes the complexity of the clotting process and illustrates the interaction between coagulation factors and the cell surfaces of platelets in what has been described as the cellular model of hemostasis. Four sequential and interrelated stages include initiation, amplification, propagation, and stabilization as shown. This model also combines multiple aspects of the classic waterfall/cascade model and further explains additional aspects of hemostasis that the classic acellular model does not. Abbreviations: TF, tissue factor; VWF, von Willebrand factor. *Derived from Monroe DM, Hoffman M. What does it take to make the perfect clot? Arterioscler Thromb Vasc Biol. 2006;26:41-48.*

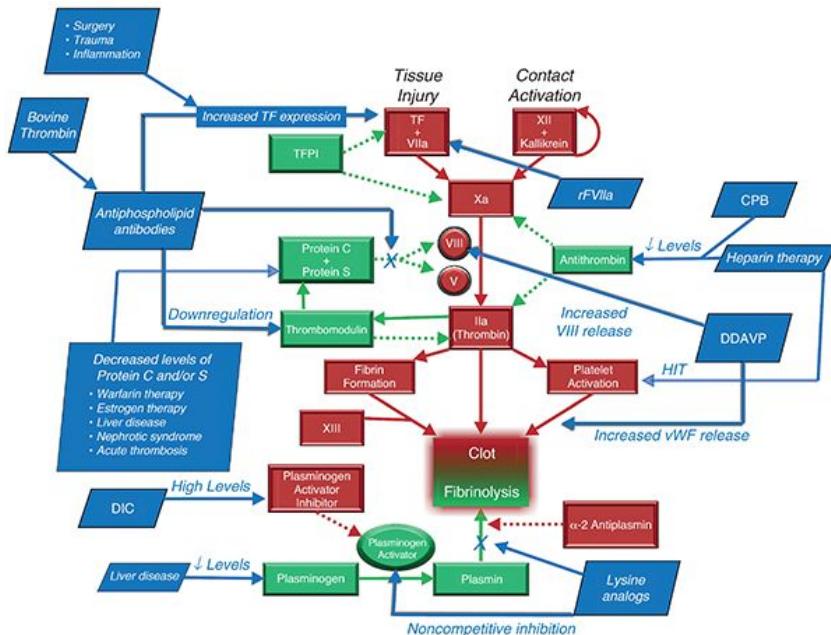


FIGURE 27.2 Procoagulant forces (red) and natural anticoagulant/fibrinolytic forces (green) and diagrammed. Dashed lines indicated an inhibitory effect. Acquired risk factors are presented in blue boxes with white lettering and arrows indicating the mechanism for the hypercoagulable effect. “Xs” denote a specific block in a pathway. Note that some acquired risk factors have multiple effects; see text for full details. Abbreviations: CPB, cardiopulmonary bypass; DDAVP, desmopressin; DIC, disseminated intravascular coagulation; HIT, heparin-induced thrombocytopenia; rFVIIa, recombinant human factor VIIa; TF, tissue factor; TFPi, tissue factor pathway inhibitor; vWF, von Willebrand factor. Modified with permission from Sniecinski RM, Hursting MJ, Paidas MJ, et al. Etiology and assessment of hypercoagulability with lessons from heparin-induced thrombocytopenia. Anesth Analg. 2011;112(1):46-58. Copyright © 2011 International Anesthesia Research Society.

Hemostasis and History

The term **hemostasis** essentially means to stop bleeding and refers to the physiologic process that keeps blood within damaged blood vessels, the opposite of hemorrhage. Multiple mechanisms are involved in hemostasis, a process critical for survival. The elucidation of models to explain the molecular and cellular interactions of the clotting cascade continue to evolve over time. The best understood clotting cascade is the waterfall/cascade model that most clinicians learned in medical school and was developed about 50 years ago but is still used as an educational tool.¹ However, this acellular model does not tell the entire story and was previously refined by Hoffman and Monroe² in their cell-based model that focuses on both cellular and humoral interactions and (see [Figure 27.1](#)). Hemostasis is also a complex inflammatory response that provides host defense mechanisms to prevent exsanguination following injury, trauma, and/or surgery. Many of the hemostatic factors have complex inflammatory signaling properties that orchestrate further host defense mechanisms, healing, and a multitude of other functions. There are multiple aspects of the physiology of hemostasis and clot formation that will be considered separately.

Initiation of Coagulation

Initiation of coagulation by procoagulant activities has been traditionally separated into extrinsic, intrinsic, and common pathways. However, a better understanding of the complex interactions has created a better conceptual integration of these pathways. Following tissue injury and vascular endothelial disruption, activation of hemostasis occurs by tissue factor (TF) expression on the subendothelial vascular basement of the blood vessel as shown in [Figures 27.1](#) and [27.2](#).¹⁻³ The TF is a transmembrane receptor expressed by

perivascular/vascular cells that binds factor VIIa.⁴ Vascular injury with loss of normal endothelial function allows for expression of extravascular TF and initiation of clotting.⁴ The TF is also present in the circulation as microparticles that are small membrane vesicles that appear following cellular injury or death and may contribute to thrombosis with sepsis or other procoagulant states. Activated factor VII (factor VIIa), a serine protease that circulates in blood in low concentrations, allows for formation of the factor VIIa/TF complex, and conversion of factor X to factor Xa.^{1,3} Subsequently, factor Xa (also a serine protease) generates trace amounts (0.1-1 nM) of thrombin.^{1,3} Thrombin generation is subsequently amplified by other coagulation factors from the intrinsic cascade that includes factor XI-, IX-, and VIII-dependent activities, although both the extrinsic (factor VIIa/TF) and intrinsic (factors IXa/VIIIa) tenase complexes produce factor Xa, which is also an important target for many anticoagulation agents. “Tenase” is a contraction of the words “ten” and the suffix “-ase” and refers to these factor complexes that activate inactive factor X through enzymatic cleavage. Multiple factors influence the degree of activation including the local TF concentration and type of cell surface supporting enzyme/cofactor complex assembly as platelets also will contribute to this response.^{1,3} The interaction of both cellular and plasma-dependent mechanisms generates the prothrombinase complex (factors Xa, Va, and prothrombin) assembly that enzymatically cleaves prothrombin to produce thrombin, another critical factor targeted in anticoagulation therapy. The orchestration of hemostasis and factors influencing its balance are shown in [Figures 27.1](#) and [27.2](#).

As part of the activation, there are also checks and balances in the system to prevent an over exuberant prothrombotic effect from occurring and regulate thrombin generation to localize clot at the site of vascular injury as shown in [Figure 27.2](#). Tissue factor pathway inhibitor (TFPI) neutralizes factor Xa when it is in a complex with TF-factor VIIa.^{1,3} The other regulator of TF-triggered procoagulant response is antithrombin (formerly called antithrombin III; a serine protease inhibitor), which circulates at a high concentration (150 µg/mL, ~2.7 µM) and neutralizes the initially formed factor Xa and thrombin.^{1,3} Overall factor VIIa patrols the circulation in search of sites of vascular injury where TF is exposed, and trace quantities of factor Xa and thrombin initiate a procoagulant response. Plasma levels of the different coagulation proteins are listed in [Table 27.1](#).

TABLE 27.1

Plasma levels and half-lives of coagulation factors^a

Factor	Level (µM)	Half-life (hours)
Fibrinogen	7.6	72-120
Prothrombin	1.4	72
Factor V	0.03	36
Factor VII	0.01	3-6
Factor VIII	0.00003	12
Factor IX	0.09	24
Factor X	0.17	40
Factor XI	0.03	80
Factor XIII	0.03	120-200
von Willebrand factor	0.03	10-24
Protein C	0.08	10
Protein S	0.14	42
Antithrombin	2.6	48-72

^aModified with permission from Tanaka KA, Key NS, Levy JH. Blood coagulation: hemostasis and thrombin regulation. *Anesth Analg*. 2009;108(5):1433-1446. Copyright © 2009 International Anesthesia Research Society.

Propagation of Coagulation

Platelets further amplify or potentially initiate clot formation at the site of vascular injury. Inflammatory cells all contain adhesion molecules to facilitate binding in the rapid flow of blood vessels as shown in [Figure 27.1](#). Following vascular injury and exposure of the subendothelial vascular basement membrane, von Willebrand factor (vWF) that circulates in a multimeric form binds to the damaged blood vessel. Platelets then adhere to subendothelial collagen-vWF via their glycoprotein Ib receptors and are activated. Thrombin generation that also occurs locally is a potent activator/agonist for platelets by stimulating protease-activated receptor (PAR)-1 and PAR-4.^{1,3} Thrombin activation of platelets further amplifies clot formation by multiple mechanisms. Platelet glycoprotein Ib receptors bind to factor XI, and they also localize factor VIII to the site of endothelial disruption via its carrier protein vWF.⁵ Also, factor V is released from platelet α -granules upon platelet activation, and factors XI, VIII, and V further amplify and sustain procoagulant responses (the “intrinsic pathway”) after thrombin-mediated activation. The serine protease factor XIa mediates the activation of factor IX to factor Xa, and factor VIIIa serves as a cofactor to factor IXa. Factor IXa, a serine protease, activates factor X to factor Xa, and factor Va serves as a cofactor to factor Xa.^{1,3} In the absence of factor VIIIa or factor IXa, as is clinically observed in hemophilia A or B, the initiation of coagulation is normal, but amplification/propagation is altered. Patients with hemophilia clot, but they develop bleeding in muscle and joints due to low TF expression.

Tissue Factor, Thrombin, and Fibrin(ogen) in Clot Formation and Stability

When generated, thrombin facilitates the proteolytic conversion of circulating soluble fibrinogen to an insoluble fibrin meshwork. This complex mechanism involves the cleavage of *N*-terminal peptides from fibrinogen, end-to-end polymerization of fibrin monomers to protofibrils, and lateral aggregation of protofibrils to fibers.^{1,3} Fibrin’s biophysical characteristics provide extensive structural support to the clot; individual fibers can be strained >330% without rupturing. The fibrin network that forms can be influenced by many different factors including fibrin(ogen)-binding proteins (eg, factor XIII), thrombin, and fibrinogen present during fibrin formation.

Role of Fibrinogen

Fibrinogen is a critical protein for clot formation and has a critical role in hemostasis.⁶ Fibrinogen is critical for clot formation and creating the dense lattice structure as shown in [Figure 27.3](#). Fibrinogen also binds to platelet glycoprotein IIb/IIIa receptors to facilitate clot formation and is affected by many antiplatelet agents. In addition, fibrinogen facilitates the cross-linking and network formation for clot and the subsequent fibrin polymerization that is catalyzed by thrombin and thrombin-activated factor XIII that locally at the site of activation. Of all the coagulation factors, fibrinogen circulates at the highest concentration (7.6 μ M, ~200-400 mg/dL). In pregnancy and during acute inflammatory responses that often occur postoperatively, fibrinogen is an acute-phase reactant.⁶ Platelets that are activated by multiple agonists express glycoprotein IIb/IIIa receptors. Thrombin catalyzes the conversion of fibrinogen to fibrin monomers after thrombin cleaves the fibrinopeptides from the fibrinogen Aa and B3 chains. Platelets that are activated release factor XIII A subunits that further polymerize fibrin monomers into fibrin. Activated factor XIII also cross-links α_2 -antiplasmin to fibrin, making fibrin more resistant to degradation. Thrombin released locally modulates the thickness and the fibrinolytic resistance of fibrin fibers.

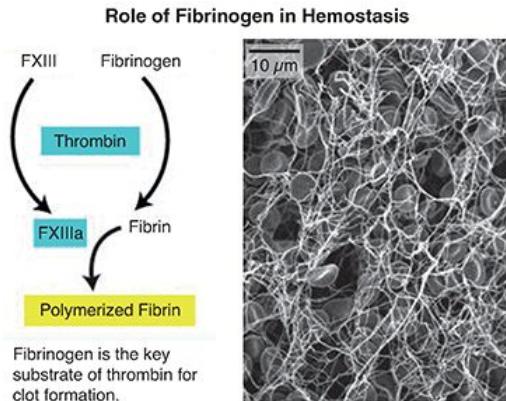


FIGURE 27.3 Fibrinogen is converted to fibrin that polymerizes by the action of thrombin. The electron micrograph shows a fibrin clot with red blood cells trapped. Platelets also are critical to fibrin formation, but they are 8 to 10 microns and not visible in the photo. Fibrinogen receptors on the platelet surface (called **IIb/IIIa receptors**) facilitate the lattice network of fibrin formation. Factor XIII, a transglutaminase, is also important for cross-linking the fibrin clot to create a stronger clot that is resistant to fibrinolysis. *Modified with permission from Tanaka KA, Key NS, Levy JH. Blood coagulation: hemostasis and thrombin regulation. Anesth Analg. 2009;108(5):1433-1446. Copyright © 2009 International Anesthesia Research Society.*

Thrombin generation is critical to clot formation, platelet activation, and fibrinogen cross-linking.^{1,3} With normal hemostatic function, the peak thrombin level reaches 200 to 500 nM, facilitating the formation of a dense fibrin network for normal clot function and hemostasis. However, in patients with hemophilia and other bleeding abnormalities, lower levels of thrombin generation occur, and as a result, clot formation is altered; thus, hemophiliacs commonly bleed into joints. Thrombin generation at the junction of the injured vasculature and subendothelial basement membrane is amplified by platelet activation and release of procoagulant microparticles.^{1,3} Thrombin has a complex effect of releasing tissue plasminogen activator (tPA) to simultaneously initiate fibrinolysis. This occurs not only by binding to thrombomodulin but also by activated factor XIII and activation of thrombin-activatable fibrinolysis inhibitor (also called TAFI). Fibrin polymerization, thrombin, and activated factor X generated at the site of vascular injury site are released systemically.

Critical Factor Levels for Hemostasis

A critical question is what levels of fibrinogen, platelets, and other coagulation proteins are necessary to optimize hemostasis in the surgical patient. Because of the critical role of fibrinogen for clot formation, current guidelines recommend fibrinogen levels of at least 1.5 to 2.0 g/L (150-200 mg/dL) for treating bleeding, and potentially even higher, as further normalization of fibrinogen to levels more consistent with normal circulating concentrations of 2 to 3 g/L (200-300 mg/dL) may be important for adequate hemostasis.⁷

Role of Factor XIII

Factor XIII plays a major role in the terminal phase of the clotting cascade that promotes formation of cross-linked fibrin polymers and generation of a stable hemostatic plug.⁸ Factor XIII exists as a tetrameric precursor (zymogen) of 2A and 2B subunits and is converted into an active transglutaminase (factor XIIIa) by thrombin and calcium.⁸ In this activated form, factor XIIIa mechanically stabilizes fibrin and protects it from fibrinolysis. As a result, patients with a deficiency in factor XIII develop a rare but severe bleeding disorder.⁸ A congenital deficiency in factor XIII is clinically defined as a plasma level of less than 5% of the protein.⁸ Most cases of factor XIII deficiency are due to lack of the A subunit with less than 1% factor XIII activity. Congenital factor XIII deficiency is inherited as an autosomal recessive disease and was first reported in Switzerland in 1960.⁹ The incidence of factor XIII deficiency is currently estimated as 1 in 3 to 5 million

births in the United States.⁸ An acquired deficiency in factor XIII can arise from the development of antibodies against factor XIII.

Role of Platelets and von Willebrand Factor

Platelets adhere to sites of vascular injury and to each other by direct and indirect effects that are part of a complex cellular mechanism required for hemostasis. Although platelet aggregation is mediated in part by bridging/binding of the integrin glycoprotein IIb/IIIa on platelet surfaces by the adhesive protein fibrinogen, this process is far more complex than simple interactions and the lattice formation of the two elements.¹⁻³

There are multistep adhesion processes involving distinct receptors and adhesive ligands that are also dependent on flow conditions, especially with the critical role of platelet function in arterial hemostatic mechanisms. Thus, following vascular injury, the subendothelial surface is exposed which then binds to vWF that is synthesized in the endothelium and critical for platelet adhesion in arteries and arterioles that have high shear rates.^{1,10}

The vWF is critical to facilitate platelet adhesion in rapid blood flow environments. The vWF binds to an adhesion ligand, its platelet membrane receptor, glycoprotein Ib-IX-V. Once platelets adhere, they are activated by a complex series of steps including release of adenosine diphosphate and thromboxane A₂, agonists that activate additional platelets and bind P2Y12 receptors and express IIb/IIIa receptors.¹¹ These important receptors are the target of common pharmacologic agents including clopidogrel, prasugrel, and ticagrelor. Platelets provide a catalytic membrane surface for further thrombin generation and clot formation and mediate additional platelet and leukocyte recruitment by mechanisms that include release of microparticles that mediate leukocyte-leukocyte and leukocyte–endothelial cell interactions. When activated, platelets may also form occlusive thrombi in cardiovascular diseases that result in myocardial infarction, stroke, or other acute ischemic syndromes of other organs.¹¹

Endothelial Regulation of Coagulation

The vascular endothelium provides an extensive interface that is critical for both anticoagulant and procoagulants functions as shown in [Figure 27.2](#).¹²⁻¹⁵ Increased shear forces and flow across the endothelium release important anticoagulation agents ([Table 27.2](#)) that include a diverse series of molecules, including nitric oxide, prostacyclin, and ecto-adenosine diphosphatase that degrade the platelet agonist adenosine diphosphate. Additionally, endothelium-derived TFPI is localized on the surface of vascular endothelium and reduces the procoagulant activities of the TF–factor VIIa initiation step.¹³ Heparin sulfate is located on endothelial surfaces and binds antithrombin in the circulation to further provide anticoagulant activity on the vascular surface. Thrombin is scavenged to keep thrombin activity local at the site of vascular injury by another endothelium-bound protein called **thrombomodulin**.¹³ A recombinant form of thrombomodulin is used clinically in Japan for disseminated intravascular coagulation (DIC) and was studied for the treatment of sepsis. Endothelial activation also provides anticoagulation by releasing tPA from the endothelial stores of the Weibel-Palade bodies. The tPA activates plasmin from plasminogen, which, in turn, promotes fibrinolysis, a critical component of vascular patency.¹³

TABLE 27.2
Endothelial proteins and mediators of hemostasis

ADAMTS13
Endothelial protein C receptor
Glycocalyx
Heparan sulfate
Nitric oxide
Plasminogen activator inhibitor 1
Prostacyclin
Protein C
Protein S

Thrombomodulin

Tissue factor

Tissue factor pathway inhibitor

Tissue-type plasminogen activator

von Willebrand factor

Abbreviation: ADAMTS13, *a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13.*

The endothelium is critical for procoagulant effects as well.¹²⁻¹⁵ Endothelial damage following vascular injury or inflammatory responses initiates an array of procoagulant responses that include release of TF, vWF, plasminogen activator inhibitor 1, and PARs. The TF as discussed is critical for initiation of clot formation and thrombin generation. The vWF allows for platelets to bind and activate locally at the site of vascular injury. Plasminogen activator inhibitor 1 prevents plasmin generation and fibrinolysis or clot cleavage. The PARs further signal platelet and a host of other responses by thrombin and other inflammatory mediators.¹²⁻¹⁵

This complex equilibrium of hemostasis continues and is constantly scavenged by many of these important mechanisms to localize hemostasis to the site of vascular injury through this multitude of regulatory mechanisms. Thrombin that is scavenged and bound to thrombomodulin is an important step in the generation of the anticoagulant protein C and TAFI.¹²⁻¹⁵ Activated protein C has multiple antiinflammatory and cytoprotective functions by modulating endothelial protein C receptor and PAR-1 (thrombin receptor).¹⁶⁻¹⁸ The TAFI also exerts antiinflammatory effects by cleaving bradykinin and C5a. Activated protein C has also seen therapeutic use as a therapy in sepsis, along with antithrombin.

Other important factors in hemostatic regulation include the circulating release of vWF that circulates as a multimer complex and is a key adhesive protein for platelets as further discussed in the following text. The vWF is also increased during inflammation and is downregulated by ADAMTS13 (*a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13*), which is also synthesized by endothelial cells.¹⁹ In addition to von Willebrand disease, other vWF abnormalities can occur due to increased degradation that occurs with ventricular assist devices or aortic stenosis, or decreased regulation due to lack of the cleaving enzyme that can occur with hemolytic uremic syndrome or thrombotic thrombocytopenic purpura.

Antithrombin and Proteins C and S

As discussed earlier, thrombin generation for hemostasis is localized because anticoagulant activities of endothelial cells modulate thrombin and other procoagulant proteases as shown in [Figure 27.2](#).²⁰ Other proteins including antithrombin, protein C, and protein S are also important serine proteases that exert anticoagulant and antiinflammatory activities. Protein C circulates in the inactive state in plasma at concentrations of 4 to 5 µg/mL (~0.08 µM) and is proteolytically activated by thrombin to activated protein C.²⁰ Thrombin is again scavenged by binding to endothelial thrombomodulin, activating protein C. Activated protein C binds protein S, and together, they function as a critical anticoagulant by inhibiting factor Va and factor VIIIa, two cofactors in thrombin generation and clot formation (see [Figure 27.2](#)). Activated protein C has been studied in sepsis but is no longer available for that indication.

Inflammation and Coagulation: An Important Link

Coagulation is closely linked to inflammatory responses through complex networks of plasma and cellular components including proteases of the clotting and fibrinolytic cascades.^{21,22} Hemostatic initiation, contact activation, and other pathways amplify inflammatory responses and can collectively produce end-organ damage in the process of their normal function as host defense mechanisms. Coagulation is activated as a central element of both a local and a systemic response to inflammation.²² Surgical injury and additional activation that can occur following cardiopulmonary bypass produces inflammatory responses initiated by contact of blood with the damaged vasculature and other nonendothelial extracorporeal circuits. In vascular

surgical and trauma patients, ischemia-reperfusion injury of organs can also occur.²³ The TF has important proinflammatory effects mediated by thrombin, plasmin, and other proteases.^{21,22,24}

Coagulation Testing

The two tests most frequently used in the perioperative setting, other than blood counts, include the prothrombin time used to evaluate the extrinsic coagulation cascade and the activated partial thromboplastin time, used to evaluate the intrinsic pathway of the classic coagulation system. The prothrombin time is affected by reductions of factors VII, X, V, and prothrombin and is used to measure the effect of warfarin and other agents with vitamin K antagonist activity or the consequences of decreased synthetic activity resulting from hepatic dysfunction. Although prothrombin time is used commonly for perioperative coagulation screening, its use and target values are still controversial and often based on consensus rather than supportive data. Clinical hemostasis may not be adequately evaluated with prothrombin times alone as is apparent in patients with hemophilia who have isolated factor VIII or IX deficiency despite normal prothrombin times.

The partial thromboplastin time is another widely used coagulation test that assesses the intrinsic coagulation cascade. Most partial thromboplastin times are activated using an agent such as ellagic acid, kaolin, or celite.²⁵ The partial thromboplastin time is used to monitor lower doses of unfractionated heparin (up to ~1.0 unit/mL), argatroban, and bivalirudin. At higher heparin concentrations used during cardiac surgery the activated clotting time is used.

Although these coagulation tests are used to evaluate bleeding, they only examine specific components of the overall coagulation cascade and may not be useful to determine the exact cause of the coagulopathy. As should be apparent from the discussion in this chapter, multiple factors influence normal coagulation and lead to coagulopathy in a perioperative setting including hemorrhage and dilution, fibrinolysis, hypothermia, and vascular injury.²⁶ These in vitro laboratory tests do not include the important interaction of platelets with coagulation factors or measurement of the stability of a hemostatic plug as these tests actually measure initial clot formation alone.

Whole blood viscoelastic tests including thromboelastography and thromboelastometry provide multiple insights into coagulation factor interaction and allow assessment of individual characteristics of either individual limbs of hemostasis or global monitoring of coagulation, and they have been widely used in the perioperative and trauma setting.²⁷ The commonly used thromboelastometric variables include coagulation time (in seconds), clot formation time (in seconds), angle (in degrees), maximum clot firmness (in millimeters), and lysis time (in seconds). Coagulation time represents the onset of clotting, whereas clot formation time and angle both represent the initial rate of fibrin polymerization. Maximal clot firmness is a measure of the maximal viscoelastic strength of clot. Lysis time is used for the diagnosis of premature lysis or hyperfibrinolysis.

Perioperative Changes in Coagulation

In surgical patients, there are multiple perioperative events that influence hemostatic function and produce coagulopathy. Vascular and tissue injury are important contributors to bleeding, but with significant hemorrhage and resuscitation with crystalloids/colloids, a dilutional coagulopathy can occur resulting from significant reductions in platelet counts/dilutional thrombocytopenia and factor deficiencies. The end result is a multifactorial reduction of thrombin generation, hypofibrinogenemia, and lack of other factors that reduce clot formation and this state is accompanied by increased fibrinolysis. The poorly formed fibrin clot contributes to bleeding, and increasing hemodilution simultaneously leads to a reduction in important proteins that balance hemostasis and anticoagulation, including antithrombin, TFPI, protein C, protein S, and thrombomodulin.²⁰ These complex hemostatic changes also contribute to the coagulopathic state.

Hemostatic Therapy

When perioperative bleeding occurs, we use red blood cells and hemostatic factors that include plasma/fresh frozen plasma, platelet concentrates, and cryoprecipitate (see further discussion in [Chapters 28](#) and [29](#)). Postoperatively, an important anabolic state occurs that increases hemostatic factors for several days. Many of the factors that modulate this acute inflammatory response postoperatively will increase cytokines and other

important signaling molecules that will increase cellular and protein synthesis. These changes will increase bone marrow production of red blood cells and platelets; increase fibrinogen and vWF; and create a hypercoagulable, procoagulant response. This is important and also integral to the current practice of use of anticoagulation for postoperative venous thromboembolic prophylaxis because of the increased thrombotic potential postoperatively.

Postoperative Hypercoagulability

The complex balance in hemostatic function can be readily altered in the postoperative setting. Because of loss of vascular endothelial function and other prohemostatic changes, venous and arterial thromboembolic events increase with age.²⁰ Acute myocardial infarction and thrombotic stroke can occur following disruption of atherosomatous plaques in coronary and cerebral arteries. The rupture of a lipid core expresses multiple procoagulant molecules that expose TF, lead to thrombin generation, and activate platelets, all leading to coagulation. Embolic and other thrombotic events occurring locally at the site of an atherosclerotic plaque can result in myocardial infarction and ischemic stroke. Additional abnormalities present in cancer patients can also initiate coagulation and other prothrombotic events that increase the risk of venous thromboembolic events.

Congenital coagulation factor deficiencies or polymorphisms of critical proteins including hemophilia A or B, vWF, antithrombin, protein C, protein S, factor V Leiden, and prothrombin (polymorphisms) are more uncommon in the perioperative period but do occur and often require specific management strategies—these conditions can present with either bleeding or thrombosis. Acquired or congenital absence of the anticoagulant proteins reduces normal clot formation and regulation, and untreated patients are at an increased risk for venous thromboembolic problems, including pulmonary embolism. A more common occurrence is the antiphospholipid syndrome that is caused by the lupus anticoagulant, which is a phospholipid-binding antibody. Of note is that patients may present with prolonged prothrombin times and partial thromboplastin times, but they are actually hypercoagulable.²⁰

Disseminated Intravascular Coagulation

The DIC is a coagulation disorder that occurs when pathologic activation of the hemostatic systems occurs following major tissue injury associated with trauma; sepsis due to bacterial, fungal, or viral causes; or other complex occurrences of vasculopathy that occurs in eclampsia.^{28,29} Activation of the coagulation system occurs; however, the multiple endothelial and circulating anticoagulation mechanisms that are part of hemostatic mechanisms are unable to inhibit systemic thrombin formation. The pathophysiologic changes of DIC include hemostatic activation characterized by microvascular deposition of clot/fibrin and thrombotic microangiopathy. Platelets are also activated and are sequestered into the pulmonary, renal, hepatic, and other organs, depleting platelets, fibrinogen, antithrombin, and other hemostatic factors. The end result is an imbalance, resulting in either a hemorrhagic coagulopathy or procoagulant state. The diagnosis of DIC is based on clinical and laboratory findings that follow.

Thrombocytopenia occurs in DIC due to the mechanisms described; however, in the perioperative setting and in critically ill patients, thrombocytopenia is common. The most common cause of perioperative thrombocytopenia is the dilutional effect following volume resuscitation; nonetheless, current strategy is to treat massive transfusion coagulopathy in the setting of trauma and surgery, and this strategy includes the administration of platelets and other clotting factors (platelets, fresh frozen plasma, and/or cryoprecipitate). Coagulation factors are also decreased in DIC, and this presents clinically with prolonged prothrombin times or activated partial thromboplastin times. In DIC and other similar syndromes, such as thrombotic thrombocytopenic purpura and hemolytic uremic syndrome, decreased levels of the protease ADAMTS13 can occur. This protease converts ultralarge von Willebrand multimers in plasma that are otherwise prothrombotic. The uncleaved multimers increase vascular platelet sequestration and the subsequent development of thrombotic microangiopathy and organ dysfunction.^{28,29} Fibrinogen levels are also used in diagnosing DIC, but, despite consumption, plasma levels are affected by multiple factors and may only detect severe cases of DIC.²⁹ D-dimers are also used in the diagnosis of DIC and are fragments of cross-linked fibrinogen that are cleaved by fibrinolysis. D-dimer levels are increased not only in DIC but also with venous

thromboembolism and following any recent trauma or surgery; thus, they may not be helpful in the surgical patient. Finally, antithrombin levels decrease in DIC and have been suggested as a therapeutic target to replete. Overall, in DIC, removal of the underlying source of the problem, treatment with antibiotics for infections, and perhaps instituting anticoagulation in efforts to reduce further consumption of coagulation factors are critical considerations.^{28,29}

Conclusion

The physiology of coagulation and hemostatic regulation are critical homeostatic mechanisms that are critical to survival. The interaction of the vasculature with both circulating plasma proteins and platelets is important for understanding the physiology of the hemostatic system, and the ability to modulate hemostasis and respond to vascular injury. Multiple disease states including atherosclerosis, acquired coagulation deficiencies, and the pharmacologic effects of many therapies used for atherosclerotic vascular disease may contribute to the problems of perioperative hemostatic management. Our goal is to reduce bleeding without the adverse effects of thrombosis. This concern is complicated by the interaction of coagulation and subsequent inflammatory responses. As discussed in the other chapters on coagulation that follow, pharmacologic interventions, based on the authors' understanding of the physiology of hemostasis, it is critical for the perioperative management and further discussed in other chapters.

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Blood Products and Blood Components

Jerrold H. Levy

In 2015, 11.3 million whole blood and red blood cells (RBCs), 2.1 million apheresis platelets, and 3.6 million plasma components were transfused.¹ While blood transfusions are considered to be standard of care in perioperative management, overall data supporting their efficacy has never been demonstrated in a prospective controlled clinical trial in the manner that drugs are approved for clinical use. For surgical patients, the relative benefit/risk of transfusions has become part of informed consent because blood products have risks, costs, supply, and inventory considerations.

Reports of adverse events including transfusion fatalities from both the Serious Hazards of Transfusion assessments in the United Kingdom and the U.S. Food Drug Administration (FDA) Center for Biologics Evaluation and Research evaluations in the United States suggest that transfusion-related deaths appear to be declining.^{1,2} Previous hemovigilance reports including the Serious Hazards of Transfusion evaluations reported that transfusion-related acute lung injury (TRALI) was the most common cause of mortality and morbidity associated with transfusion. However, recent data reported from 2013 to 2017 noted that transfusion-associated circulatory overload (TACO) cases caused the highest number of reported fatalities (32%), followed by the combined TRALI and possible TRALI (30%).¹ Less common causes reported included microbial contamination (12%), hemolytic transfusion reactions due to non-ABO incompatibilities (11%) and ABO incompatibilities (7%), anaphylactic reactions (6%), and hypotensive reactions (2%).¹ Of note is that both known risks and ongoing potential for new viral contaminants (unknown risks) are likely associated with transfusion.

However, as reported to the FDA, the blood supply is safer today than at any time in history which is due to ongoing advances in donor screening, improved testing, automated data systems, and efforts at blood conservation and patient blood management that have changed transfusion medicine practices.¹ As a result, in 2015, there was a 14% decrease in transfusions of RBCs and whole blood in the United States since 2013.¹ Nonetheless, despite the relative safety of our blood supply, transfusions have the potential for adverse events including infections and multiple other adverse events that include increased hospital and intensive care unit (ICU) length of stay. Of importance is that most data and studies evaluating transfusions are based on retrospective studies and include observational data from critically ill patients already predestined to adverse outcomes. Other important issues that transfusions pose in addition to the risks are the costs and blood inventory required for managing patients. Patient blood management initiatives have evolved from ongoing work by many different interests to develop evidence-based transfusion practices and strategies to reduce bleeding and the need for allogeneic transfusions. In the perioperative setting, multiple specialties and health care providers influence the decision to transfuse a patient. Most blood conservation strategies focus on RBC transfusions and specific hemoglobin concentration thresholds with far less emphasis on coagulation factors whose effects are more difficult to measure. Because the decision to transfuse a patient is complex, rarely can a single laboratory value be an absolute indicator of the need for transfusion. Decisions to transfuse require multiple clinical considerations including risk factors, comorbidities, hemodynamic stability, and the rate of bleeding, especially in hemorrhagic shock, a common perioperative emergency.

The appropriate use of blood products, including RBCs, fresh frozen plasma (FFP), cryoprecipitate, or platelet transfusions, continues to be defined in surgical and trauma patients. In European countries, purified factor concentrates are increasingly used instead of transfusion factors that include fibrinogen and prothrombin complex concentrates (PCCs). Guidelines for bleeding management and transfusions in surgical and trauma patients have been reported, including those from the American Society of Anesthesiologists as noted in **Table 28.1**.³⁻⁵

As a reminder, before the elective transfusion of RBCs, crossmatching occurs. This process is performed by mixing the patient's blood sample after an antibody screen for blood type with a sample of RBCs from the donor unit using a section of tubing from the blood bag. The blood after mixing is examined for hemolysis and/or clumping (also called agglutination), which would signify a positive test result and the presence of an additional antibody.

Blood products are administered routinely in perioperative bleeding management. Despite guidelines, most physicians either have not read the guidelines or have difficulty following them. Clinicians often resort to empiric therapy because laboratory tests may be difficult to obtain or take too long to obtain results, do not determine platelet defects, or due to concerns about obtaining blood products from the blood bank in a timely fashion for high-risk patients. The role of transfusion in massive transfusion protocols following trauma and/or major hemorrhage will be considered in a separate chapter. However, in a critically ill patient, the importance of a multimodality approach is important rather than focusing on the individual transfused components.

The American Society of Anesthesiologists established the Task Force on Blood Component Therapy to develop evidence-based guidelines for transfusing RBCs, platelets, FFP, and cryoprecipitate in perioperative settings. Specific guidelines were developed according to a defined methodology.⁵ The recommendations of the task force were reported and can be found in [Table 28.1](#). Although these guidelines are reported as recommendations, there are also other important considerations regarding the use of specific blood units in surgical patients that need to be considered. The rationale for transfusion of individual blood components will also be considered.

TABLE 28.1

Recommendations for transfusion of non-red blood cell products****

Platelets

- Platelet transfusion may be indicated despite an apparently adequate platelet count or in the absence of a platelet count if there is known or suspected platelet dysfunction (*e.g.*, the presence of potent antiplatelet agents, cardiopulmonary bypass, congenital platelet dysfunction, and bleeding)[†]
- In surgical or obstetric patients, platelet transfusion is rarely indicated if the platelet count is known to be greater than $100 \times 10^9/l$ and is usually indicated when the count is less than $50 \times 10^9/l$ in the presence of excessive bleeding.

Plasma products (*e.g.*, FFP, PF24, or thawed plasma)[‡]

- FFP is indicated:
 - For correction of excessive microvascular bleeding (*i.e.*, coagulopathy) in the presence of an INR greater than 2.0, in the absence of heparin
 - For correction of excessive microvascular bleeding secondary to coagulation factor deficiency in patients transfused with more than one blood volume (approximately 70 ml/kg) and when PT or INR and aPTT cannot be obtained in a timely fashion
 - For urgent reversal of warfarin therapy when PCCs are not available
 - For correction of known coagulation factor deficiencies for which specific concentrates are unavailable
- FFP is not indicated:
 - If PT or INR and aPTT are normal
 - Solely for augmentation of plasma volume or albumin concentration
 - Administer FFP in doses calculated to achieve minimum of 30% of plasma factor concentration. Four to five platelet concentrates, 1 unit single-donor apheresis platelets, or 1 unit fresh whole blood[§] provide a quantity of coagulation factors similar to that contained in one unit FFP

Cryoprecipitate

- Cryoprecipitate is indicated:
 - When a test of fibrinogen activity indicates a fibrinolysis
 - When the fibrinogen concentration is less than 80-100 mg/dl in the presence of excessive bleeding^{||}
 - As an adjunct in massively transfused patients when fibrinogen concentrations cannot be measured in a timely fashion

- For patients with congenital fibrinogen deficiencies
- Whenever possible, decisions regarding patients with congenital fibrinogen deficiencies should be made in consultation with the patient's hematologist
- Transfusion of cryoprecipitate is rarely indicated if fibrinogen concentration is greater than 150 mg/dl in nonpregnant patients.
- Treat bleeding patients with von Willebrand disease types 1 and 2A with desmopressin and subsequently with specific VWF/FVIII concentrate, if available. Cryoprecipitate should be administered if there is no response to or availability of desmopressin or VWF/FVIII concentrate
- Treat bleeding patients with von Willebrand disease types 2B, 2M, 2N, and 3 with specific VWF/FVIII concentrate, if available. If VWF/FVIII concentrate is not available, cryoprecipitate is indicated

Abbreviations: aPTT, activated partial thromboplastin time; FVIII, factor VIII; INR, international normalized ratio; PCC, prothrombin complex concentrate; PT, prothrombin time.

*This table displays some transfusion criteria that may suggest when to transfuse with the above blood products. The decision to apply some or all the criteria shown in this table is dependent upon the clinical context and judgment of the practitioner. The table is not intended as a mandatory or exhaustive list.

Scientific evidence is insufficient to evaluate the perioperative benefit of applying the earlier suggested criteria.

**Note current recommendations for fibrinogen repletion in the bleeding patient are targeting levels of 150–200 mg/dL or higher (as noted in [References 20, 32–35](#)).

†The proper dose of platelets should be based on recommendations of the local institutional transfusion committee.

‡The FFP refers to plasma frozen within 8 h after phlebotomy, PF24 refers to plasma frozen within 24 h after phlebotomy, and thawed plasma refers to FFP stored up to 5 days at 1°–6°C after thawing. In the United States, it is a common practice to use these terms interchangeably. In this table, the term FFP refers to the use of any of these plasma products.

§Many institutions in the United States no longer have fresh whole blood available from the blood bank.

||Cryoprecipitate may be indicated at a higher fibrinogen concentration in actively bleeding obstetric patients. Reprinted with permission from American Society of Anesthesiologists Task Force on Perioperative Blood Management. Practice guidelines for perioperative blood management: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Management. *Anesthesiology*.

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Transfusion Therapy for Bleeding

Volume replacement in the perioperative setting when there is critical bleeding requires the use of replacement therapy. Although crystalloid, colloid, and RBCs may be initially administered, none of these products provide coagulation factors including platelets and can exacerbate coagulopathy. Severe bleeding requires the use of a massive transfusion protocol that includes multiple blood products as whole blood is in nonmilitary settings may not be readily available and includes RBCs, FFP, platelets, and cryoprecipitate. With major bleeding in surgical in trauma patients, the goal is to restore circulating levels of hemostatic factors. The increasing use of point of care testing with viscoelastic assays including rotational thromboelastometry and thromboelastography. Following massive transfusion therapy, hypothermia and acidosis frequently occur, further complicating bleeding. Thus, temperature and pH must be monitored and corrected during any ongoing transfusion effort.

Red Blood Cells

There is no single minimum acceptable hemoglobin level that can be applied to all patients when deciding when to transfuse RBCs. Chronic anemia is better tolerated than acute anemia. However, with acute anemia, compensatory mechanisms that increase cardiac output and improve oxygen transport depend on the patient's cardiovascular reserve. In surgical patients with heart failure and/or flow-restricting lesions, compensation during acute anemia may be limited. Multiple factors should be considered including intravascular volume,

whether the patient is actively bleeding, and the need for improvement in oxygen transport. For instance, the patient receiving multiple inotropic agents and requiring an intra-aortic balloon pump who is anemic following surgery may need RBC transfusion to maintain a higher hemoglobin level than an otherwise healthy and hemodynamically stable patient. The decision to transfuse must weigh the risks of transfusion against the need for improved oxygen-carrying capacity in recovery from trauma, surgery, or illness.⁵ The American Society of Anesthesiologists Task Force on Perioperative Blood Transfusion and Adjuvant Therapies noted in its recommendations that transfusion of RBCs should usually be administered when the hemoglobin concentration is low (eg, <6 g/dL in a young, healthy patient), especially when the anemia is acute. The RBCs are usually unnecessary when the hemoglobin concentration is more than 10 g/dL.⁵ These conclusions may be altered in the presence of anticipated blood loss or active critical (ie, myocardium, central nervous system, or renal) or target organ ischemia. Determining whether intermediate hemoglobin concentrations (ie, 6 to 10 g/dL) justify or require RBC transfusion should be based on any ongoing indication of organ ischemia, potential or actual ongoing bleeding (rate and magnitude), the patient's intravascular volume status, and the patient's risk factors for complications of inadequate oxygenation. These risk factors include a low cardiopulmonary reserve and high oxygen consumption.⁵ Hemoglobin triggers for transfusion are not to be taken as absolute; patients with significant cardiac disease should be transfused if signs or symptoms of inadequate myocardial oxygenation appear.

Patient blood management strategies have increasingly become an area of focus to reduce allogeneic blood exposure.⁶ However, most of these strategies focus primarily on RBC transfusions and specific hemoglobin values without defining a clinically meaningful parameter that includes an appropriate clinical indicator or other meaningful threshold for RBC transfusion. Current studies that address specific hemoglobin thresholds do not examine critical physiologic parameters such as measures of oxygen delivery and/or oxygen debt.⁶ Because clinicians cannot readily measure specific oxygen delivery or oxygen debt, they treat specific hemoglobin thresholds instead. Many reported studies note that restrictive thresholds for transfusions of RBCs are noninferior to liberal thresholds in most clinical scenarios.¹

One important aspect of adverse events associated with RBC transfusion relates to the age of RBCs transfused and changes that occur in stored RBCs as they age (the so-called storage lesion).⁶⁻⁸ Although RBCs are stored for up to 42 days after donation, biochemical changes occur in RBCs as they age. Studies suggest that RBC units stored for long periods (often described as >14-21 days) may lead to adverse effects. The mechanisms for these adverse events include senescent RBC fragments, impaired nitric oxide production, and increased nitric oxide scavenging by stored RBCs, together with reduced nitric oxide synthesis by dysfunctional endothelial cells. However, many of the studies demonstrating adverse outcomes are from large retrospective studies with all of the inherent problems associated with retrospective analyses and not all studies are in agreement.

Red Blood Cell Storage Lesions

The RBCs develop a complex series of biochemical and metabolic changes during storage in the blood bank that include depletion of adenosine triphosphate and of 2,3-diphosphoglycerate, membrane phospholipid vesiculation and shedding, protein oxidation, and lipid peroxidation of the cell membrane. As the blood ages, RBCs undergo shape changes with increased fragility that may impair microcirculatory flow. Because of increased red cell–endothelial cell interaction, bioreactive lipids and other substances are released that may initiate inflammatory responses leading to TRALI, as described in more detail in the following text. These complex changes can also decrease oxygen delivery and increase hemolysis. When free hemoglobin is released from the RBC, it binds to nitric oxide, and this nitric oxide scavenging causes endothelial dysfunction and additional proinflammatory events including generation of oxygen free radicals.⁸

Red Blood Cell Storage and Tissue Oxygenation Parameters

Transfusion of RBCs is used therapeutically to increase the oxygen-carrying capacity of blood and thereby improve oxygen delivery to tissues. Multiple retrospective studies have attempted to evaluate the clinical outcomes of critically ill patients receiving fresh compared to older blood. There are multiple analyses in the

literature that examine the clinical effect of blood storage in multiple patient groups including trauma patients, ICU patients, and patients undergoing cardiac surgery or those with acute heart disease with variable effects. Most of the studies are observational based, and there is clinical equipoise regarding results and previous systematic reviews and a meta-analysis conducted in critically ill patients have been inconclusive.

The Red Cell Storage Duration Study, a prospective, randomized clinical trial of complex cardiac surgical procedures reported red-cell storage was not associated with significant differences in the change in multiorgan function that compared RBC transfusions stored for 10 days or compared to RBCs stored for 21 days or more among patients 12 years of age. Other clinical studies include the TRANSFUSE trial, which reported that the age of transfused red cells did not affect 90-day mortality among critically ill adults. Although RBC transfusions are used extensively in the perioperative setting, all transfusions can be associated with adverse events.

Plasma/Fresh Frozen Plasma

Plasma is transfused for multiple indications, especially in surgical and trauma patients. Plasma use has increased with the increasing understanding of its role in managing the coagulopathy associated with massive transfusion (massive transfusion is covered in detail in a separate chapter). Currently, plasma and FFP are used to replace volume and coagulation factors during massive transfusion, to treat or prevent future bleeding during surgery and invasive procedures, to reverse warfarin therapy in patients, and for treatment of coagulation factor abnormalities where specific concentrates are not available. The FFP is plasma frozen within 8 hours of collection. However, many plasma units transfused in the United States are actually frozen within 24 hours after phlebotomy and called plasma FP24. The difference is that cryoprecipitate can be obtained from FFP but not plasma; nonetheless, experts agree that FFP and plasma can be transfused interchangeably and most clinicians refer to both products as FFP, despite this subtle distinction. Thawed plasma stored for up to 5 days before administration is also commonly used for transfusion. Plasma is used throughout the text to refer to either FFP or thawed plasma, as most scientific evidence supporting and distinctions among different plasma transfusion practices is limited.

Following collection of a unit of blood, FFP is the plasma that remains after RBC and platelet removal and contains blood coagulation factors, fibrinogen, and other plasma proteins in a volume of 170 to 250 mL that is then frozen and can be stored for up to 1 year. Most plasma administered in perioperative settings is actually FP24. Before administration, the plasma must be thawed in a water bath at 37°C, which takes about 30 minutes. After thawing, the units of FFP are stored at 1°C to 6°C and are transfused within 24 hours. The FFP should be administered through a component administration set with a 170-micron filter. If not used within 24 hours, it can be relabeled as “thawed plasma” and stored at 1°C to 6°C for an additional 4 days. Thawed plasma maintains normal levels of all factors except factor V, which falls to 80% of normal and factor VIII, which falls to 60% of normal during storage.² Because these levels are above the in vivo threshold for normal hemostatic function for these factors and factor VIII is an acute phase reactant, thawed plasma can be used as a substitute for FFP.²

The FFP is used for treating bleeding because of coagulopathies that are associated with a prolongation of either the activated partial thromboplastin time (PTT) or prothrombin time (PT)/international normalized ratio (INR) greater than 1.5 times normal, or a specific coagulation factor assay of less than 25%.⁵ The FFP is often used to reverse the effect of warfarin before surgery or during active bleeding episodes (see [PCCs](#) later in this chapter and see also [Chapter 29](#)). When FFP is indicated, it should be administered in a dose calculated to achieve a minimum of 30% of plasma factor concentration. Ten to 15 mL/kg of FFP will generally result in a rise of most coagulation proteins by 25% to 30% (or increases in 0.25-0.3 U/mL), although a dose of 5 to 8 mL/kg may be adequate to urgently reverse warfarin anticoagulation but varies based on the initial levels of the vitamin K-dependent coagulation factors.⁵ The FFP is also an important part of a transfusion algorithm for posttraumatic bleeding that is covered in more detail in the chapter on massive transfusion.

Guidelines exist in many countries for the use of plasma and include active bleeding preoperatively, invasive procedures in patients with acquired coagulation abnormalities, thrombotic thrombocytopenic purpura, and patients with a congenital coagulation factor deficiency where specific factor concentrates are

not available. Published plasma transfusion indications are listed in [Table 28.1](#). However, for immediate correction of vitamin K antagonists (eg, warfarin), four-component PCCs should be used as will be subsequently discussed.

Plasma is overused in surgery most often because of the empirical nature of transfusion therapy. The most common cause of bleeding after surgery is platelet dysfunction. Furthermore, the PT and PTT, which are widely used to evaluate bleeding, have never been demonstrated to accurately reflect the cause of bleeding in surgical patients. Indeed, the PT and PTT can be abnormal in patients who are not bleeding. Despite the widespread use of plasma, there is little evidence for its effectiveness outside of trauma patients requiring massive transfusion.^{10,11} Analyses of randomized controlled trials have been unable to demonstrate consistent evidence of benefit for plasma in most clinical scenarios.^{10–12} The use of plasma in many situations to treat elevated INRs, especially when the INR is less than 1.7 is problematic, as these patients may not be at risk for bleeding and the lowest INR obtainable with plasma is approximately 1.5 because that is the INR of plasma/FFP.¹³ A recent survey evaluating approximately 5,000 plasma transfusions reported that 43% were administered in the absence of bleeding in efforts to correct abnormal coagulation tests preoperatively or before invasive procedures, and in 31% of cases where plasma was given, the INR was 1.5 or less.¹⁴

Plasma transfusions, like all blood products, have the potential for adverse effects. A recent study reported a 6% incidence of TACO in ICU patients, which can occur when patients with heart failure/ventricular dysfunction are given as little as 2 to 4 units of plasma.^{1,15} Both TRALI and TACO are major causes of mortality and morbidity from blood transfusion.^{1,2} However, for TRALI, the incidence has declined with the use of plasma from male donors or female donors who have no history of pregnancy.^{16,17} The TRALI and TACO will be considered in more detail later.

Solvent/Detergent-Treated Plasma

Human pooled plasma that has been solvent/detergent (S/D) treated is now available commercially in a sterile, frozen solution of pooled human plasma from donors that has been treated with an S/D process. This method of preparation not only kills certain viruses and minimizes the risk of serious virus transmission but also removes other agents, including cellular debris and lipid contaminants. This process is thought to reduce the risk of TRALI. The plasma used to manufacture this product is collected from specific pools of US donors who have been screened and tested for diseases transmitted by blood and determined to be suitable donors. Collected donor pools include approximately 500 to 1,600 donors. This product is used extensively in Europe and other countries and approximately 13 million have been administered outside of the United States. In the United States, this product is indicated for replacement of coagulation factors with acquired deficiencies due to liver disease, undergoing cardiac surgery and liver transplantation, and for plasma exchange in patients with thrombotic thrombocytopenic purpura. Administration is based on ABO blood group compatibility.

The collection and testing process for this pooled and treated plasma is extensive; unlike other blood products, it is extensively purified and tested. The product is manufactured from US plasma donations that are extensively tested for viral markers with each pool limited to 630 to 1,520 individual donors. Frozen plasma units are thawed, pooled, filtered through a 1-micron pore membrane, and then treated with S/D reagents (1% tri[n-butyl] phosphate and 1% octoxynol for 1–1.5 hours at +30°C [86°F]) to inactivate enveloped viruses. The S/D reagents are removed by sequential oil and solid phase extraction procedures that also remove prions. After sterile filtration, the product is filled into blood bags, labeled, deep-frozen, and stored at 4°F. The S/D treatment step has been shown to effectively inactivate relevant pathogenic and enveloped viruses.

Leukocyte antibodies are not detected in S/D plasma because the process dilutes white blood cell antibodies and soluble human leukocyte antigens (HLAs) are present in the product, neutralizing the antibodies. This pooled and treated plasma product has not been associated with TRALI, with more than 13 million units transfused to date.

Cryoprecipitate

In the early 1960s, attempts to create an improved factor VIII concentrate led to the development of cryoprecipitate. Cryoprecipitate forms when frozen plasma is allowed to thaw slowly at 1°C to 10°C;

cryoprecipitate is rich in fibrinogen, factor VIII, and factor XIII but also contains other factors. This product was introduced as a therapy for patients with hemophilia A^{18,19}, however, its major use today is to replete fibrinogen levels during coagulopathies. Cryoprecipitate contains fibrinogen and high concentrations of factor VIII, von Willebrand factor, and factor XIII.

Cryoprecipitate is composed of the insoluble proteins that precipitate when FFP is thawed and is named for that process. The residual volume of cryoprecipitate (~15 mL) is refrozen and stored and has a shelf life of ~36 months frozen. However, once thawed, it must be used within 4 hours and cannot be refrigerated. Cryoprecipitate contains therapeutic amounts of factor VIII:C, factor XIII, von Willebrand factor, and fibrinogen. Each bag of cryoprecipitate contains 80 to 100 units of factor VIII:C, 150 to 200 mg of fibrinogen, significant amounts of factor XIII, and von Willebrand factor, including the high-molecular-weight multimers. Cryoprecipitate is used not only to increase fibrinogen levels depleted because of massive hemorrhage or coagulopathy but also for the treatment of congenital or acquired factor XIII deficiency. For fibrinogen replacement therapy, in Europe, specific fibrinogen concentrates are available (see the following text); however, 1 unit of cryoprecipitate per 10 kg body weight increases plasma fibrinogen by roughly 50 to 70 mg/dL in the absence of continuing consumption or massive bleeding.^{19,20} The minimum hemostatic level of fibrinogen is traditionally suggested to be around 100 mg/dL but normal fibrinogen levels are 200 mg/dL and higher, and higher levels of fibrinogen may be important for clot formation (see “[Fibrinogen Concentrates](#)” section). Because cryoprecipitate does not contain factor V, it should not be the sole replacement therapy for disseminated intravascular coagulopathy, which is almost always associated with a variety of factor deficiencies and thrombocytopenia. Because fibrinogen is an important determinant of hemostatic function and clot strength, fibrinogen levels should be routinely evaluated in bleeding patients especially following multiple transfusions. Hypofibrinogenemia itself can cause a prolonged PT and PTT, and FFP transfusion alone may not provide sufficient repletion. Cryoprecipitate is likely underused in cardiac surgical patients who are bleeding and “refractory” to standard FFP and platelets. Cryoprecipitate has been withdrawn from many European countries due to safety concerns, primarily the transmission of pathogens, and because it is a multidonor blood product. Instead, commercial fibrinogen preparations are available for fibrinogen replacement therapy. The fibrinogen concentrates used for repleting fibrinogen levels are free of known pathogens, stored as a lyophilized product, and can be readily administered when required. Nevertheless, cryoprecipitate remains available for hemostatic therapy in several countries, including the United States, Canada, and the United Kingdom. An adult dose of cryoprecipitate is ~10 units obtained from 10 different donors, and is equivalent to ~2 g fibrinogen.

Platelet Concentrates

Platelets that are used clinically are either pooled random-donor platelet concentrates or single-donor apheresis and can be stored for up to 5 days. In medical patients, a platelet count of 10,000/ μ L is a typical threshold for prophylactic platelet transfusion (normal platelet count ranges from 150,000 to 400,000 platelets per μ L), but the optimal platelet count or dose is still being evaluated. Consensus descriptions suggest the platelet count for therapeutic transfusions to control or prevent bleeding with trauma or surgical procedures requires a higher transfusion trigger of 100,000/ μ L for neurosurgical procedures and between 50,000/ μ L and 100,000/ μ L for other invasive procedures or trauma. Many transfused products, including platelets, undergo leukoreduction to reduce alloimmunization rates, cytomegalovirus transmission, and febrile transfusion reactions. Whether leukoreduction reduces immunomodulatory effects of transfusion (ie, decreases infection rates and cancer recurrence) is still controversial, as is the use of universal leukoreduction as the procedure, is associated with significant cost.

Platelet concentrates can be prepared either from whole blood or by apheresis. For many years, the use of platelet concentrates was the standard for platelet administration, and this required exposure to multiple donors, as 10 units of platelets required 10 different donors. An important advantage of platelets collected by apheresis is that a sufficient enough number can be collected from a single donor while an equivalent number of platelets require pooling of at least 4 to 6 whole blood-derived platelets concentrates. Reducing donor exposures by using apheresis platelets also has the potential advantages of reducing transfusion-transmitted infections and platelet alloimmunization where antibodies form because platelets have many antigens besides

ABO.^{21,22} Testing has reduced the infectious risk to low levels. The quality of apheresis platelets is similar to pooled random-donor platelets concentrates, these two products can be used interchangeably based on availability and cost considerations.^{21,22} Platelets are stored at 22°C rather than at the 4°C storage used for red cell storage and have a shelf life of ~5 days. However, there remains significant risk of bacterial infection with platelet administration because storage at 22°C is permissive for bacterial growth. Some studies have suggested a reduction in bacterial transmission by transfusion with the use of single-donor platelets.^{21,22} However, both the American College of Pathologists and the American Association of Blood Banks (AABB) have mandated testing of all platelet products for bacteria.^{21,22}

A summary of platelet transfusion recommendations as reported by the AABB are listed in [Table 28.2](#).

TABLE 28.2

Recommendations for platelet transfusions

Recommendation 1

The AABB recommends that platelets should be transfused prophylactically to reduce the risk for spontaneous bleeding in hospitalized adult patients with therapy-induced hypoproliferative thrombocytopenia. The AABB recommends transfusing hospitalized adult patients with a platelet count of 10×10^9 cells/L or less ($100,000/\mu\text{L}$) to reduce the risk for spontaneous bleeding. The AABB recommends transfusing up to a single apheresis unit or equivalent. Greater doses are not more effective, and lower doses equal to one-half of a standard apheresis unit are equally effective. (Grade: strong recommendation; moderate-quality evidence)

Recommendation 2

The AABB suggests prophylactic platelet transfusion for patients having elective central venous catheter placement with a platelet count less than 20×10^9 cells/L ($20,000/\mu\text{L}$). (Grade: weak recommendation; low-quality evidence)

Recommendation 3

The AABB suggests prophylactic platelet transfusion for patients having elective diagnostic lumbar puncture with a platelet count less than 50×10^9 cells/L ($50,000/\mu\text{L}$). (Grade: weak recommendation; very-low-quality evidence)

Recommendation 4

The AABB suggests prophylactic platelet transfusion for patients having major elective nonneuraxial surgery with a platelet count less than 50×10^9 cells/L ($50,000/\mu\text{L}$). (Grade: weak recommendation; very-low-quality evidence)

Recommendation 5

The AABB recommends against routine prophylactic platelet transfusion for patients who are nonthrombocytopenic and have cardiac surgery with cardiopulmonary bypass. The AABB suggests platelet transfusion for patients having bypass who exhibit perioperative bleeding with thrombocytopenia and/or evidence of platelet dysfunction. (Grade: weak recommendation; very-low-quality evidence)

Recommendation 6

The AABB cannot recommend for or against platelet transfusion for patients receiving antiplatelet therapy who have intracranial hemorrhage (traumatic or spontaneous). (Grade: uncertain recommendation; very-low-quality evidence)

Abbreviation: AABB, American Association of Blood Banks.

Data from Kaufman RM, Djulbegovic B, Gernsheimer T, et al. Platelet transfusion: a clinical practice guideline from the AABB. *Ann Intern Med.* 2015;162(3):205-213.

Alloimmunization

Allogeneic blood transfusions are in many ways similar to organ transplantation. Transfusing cells from one patient (the donor) to the recipient introduces multiple foreign cells, antigens, and other potential contaminants. An immunocompetent recipient often develops variable immune responses to the transfused

agents that include graft versus host disease (to be considered later in this chapter). Multiple other antigens that are not routinely crossmatched for platelets and responsible for alloimmunization include HLAs, class I shared by platelets and leukocytes and class II present on some leukocytes; granulocyte-specific antigens; platelet-specific antigens (human platelet antigen); and RBC-specific antigens. Platelets are crossmatched only to RBC-specific antigens. The spectrum of additional antigenic components in platelets is why leukoreduction is part of an important management strategy.

Leukoreduction

Leukoreduced platelet and RBC products have many potential benefits. By reducing additional leukocyte exposure, sensitization and antibody formation to different white blood cell antigens (alloimmunization) is reduced.^{21,23} Cytomegalovirus transmission is also reduced by reducing leukocyte burden, and as a result, there is also a reduction in febrile transfusion reactions.^{22,23} Other potential benefits of leukoreduction include decreased exposure to white cells that potentially contribute to immunomodulatory effects of transfusion (transfusion-related immunomodulation) that may present as increased risk for postoperative infections and tumor metastasis formation in cancer surgery. There is extensive controversy about the immunomodulatory effects of transfusions as patients often have multiple other risk factors that contribute to outcomes.^{21,23} Several countries including Canada and many medical centers have instituted universal leukoreduction of the blood supply.

Graft Versus Host Disease

In cancer patients and certain pediatric populations, platelets are irradiated to prevent transfusion-related graft versus host disease, a potentially fatal complication of transfusion. Graft versus host disease occurs more commonly after a bone marrow or stem cell transplant, or following platelet transfusions where viable white cells from the donor regard the recipient's body as foreign and create acute inflammatory responses and tissue and organ injury by attacking the recipient's body. For platelet transfusions, γ -irradiation is performed for patients receiving allogeneic stem cell transplants, for patients receiving blood products from related donors, and for patients who are severely immunocompromised, usually because of their disease or its treatment (eg, patients with Hodgkin disease or other lymphomas).^{21,22,24}

Indications for Platelet Transfusions and Transfusion Triggers

In medical patients, a platelet transfusion trigger of approximately 10,000 platelets/ μ L in efforts to prevent bleeding is often described. However, data and prospective studies to evaluate the effects of platelet dose on hemostasis and rates of platelet use overall for perioperative management are often based on consensus guidelines rather than clinical studies. There are three important areas of controversy regarding the use of platelet transfusions without active bleeding.²³ First, the optimal prophylactic platelet dose to prevent thrombocytopenic bleeding even in medical patients is not well known. Second, the exact platelet count threshold that requires transfusion of platelets is not known. Finally, whether prophylactic platelet transfusions are superior to therapeutic platelet transfusions in surgical patients is not known.

A review of clinical trials²⁵ suggests that in hematologic malignancies, a target platelet count of more than 10,000 platelets/ μ L is acceptable in preventing spontaneous bleeding caused by thrombocytopenia alone, although platelet dosing was not found to influence bleeding when administered prophylactically.^{26,27}

Guidelines for platelet transfusions exist in many countries.²⁶⁻²⁹ Hematology patients receive about two-thirds of all platelet concentrates, depending on the medical center. Additional studies are needed to determine the optimal transfusion practice; however, the clinical use of platelet transfusions to obtain hemostasis is complicated because direct platelet function testing is rarely possible in the bleeding or coagulopathic patient. For instance, after cardiopulmonary bypass, platelet counts may be normal, but platelets are functioning poorly (qualitative platelet defect). Most recommendations are to maintain platelet counts of greater than 50,000/ μ L in surgical patients; however, this is also dependent on whether the circulating platelets are functional. Although definitive data for the most effective platelet dosing strategy for maintaining perioperative hemostasis is not available, following platelet numbers is our only practical guide. However, clinicians must bear in mind that patients with abnormal platelet counts and/or hemostasis may not

bleed at the same time that patients with normal platelets counts may bleed based on the platelet dysfunction that appears in many surgical settings.

In most surgical patients, there is little data to support prophylactic platelet transfusions; the exceptions are massive transfusion coagulopathy and certain closed surgical procedures where bleeding may be highly problematic such as intracranial hemorrhage. Dilutional thrombocytopenia often occurs as an early manifestation of massive transfusion. However, studies also suggest thrombocytopenia may not always correlate with abnormal bleeding. In cardiac surgical patients, defective platelet function is part of the clinical problem, and the inability to have suitable platelet function testing for postoperative use complicates our ability to decide when to transfuse platelets.

Studies in chronic thrombocytopenic patients suggested that significant spontaneous bleeding with an intact vascular system does not occur until the platelet count is 5,000 platelets/ μ L or less.^{30,31} Previously, a platelet count of less than or equal to 20,000/ μ L was considered to be an indication for a prophylactic platelet transfusion. However, four randomized prospective transfusion trials comparing prophylactic platelet transfusion triggers of 10,000 versus 20,000 platelets/ μ L showed no differences in hemorrhagic risks. Current recommendations are that a threshold of 10,000 platelets/ μ L for prophylactic platelet transfusion be used in hematology patients who are chronically thrombocytopenic.

Platelet Counts for Surgery and Invasive Procedures

For surgery or following trauma, expert recommendations suggest that a platelet count of greater than or equal to 50,000/ μ L be maintained, although there is little data to support these recommendations. In neurosurgical patients or patients with intracerebral bleeding and for neurosurgical procedures, expert recommendations suggest that platelet counts should be maintained at greater than 100,000/ μ L. With platelet counts between 50,000 and 100,000/ μ L, clinical decisions to transfuse platelets should be based on the type of surgery, trauma, rates of bleeding, risk of bleeding, use of platelet inhibitors, and other potential coagulation abnormalities. An assessment of whether platelet function is normal should also weigh in to the decision about when to transfuse platelets.

Abnormal platelet function can arise from numerous causes, including multiple medications, sepsis, malignancy, tissue injury following trauma, obstetric issues including eclampsia, cardiopulmonary bypass, or hepatic or renal failure with azotemia/uremia. In the bleeding patient, laboratory testing can determine platelet counts but not platelet function, so bleeding due to tissue injury may occur at higher platelet counts. If platelet dysfunction is present in the face of trauma or surgery, platelet transfusions may be necessary, even in the presence of a normal platelet count. Unfortunately, there is little data to help clinicians manage these complex but common occurrences, and as a result, platelet transfusions must be guided by a logical approach that weighs each of these factors.

Purified Factor Concentrates

Fibrinogen Concentrates

Fibrinogen is a critical clotting protein, with increasing data further reporting its importance for perioperative hemostasis.^{20,32-35} Cryoprecipitate is routinely administered as the source of fibrinogen in many countries, while fibrinogen concentrates are also used in some countries. Although any biologic agent can potentially produce an adverse event, current reviews of published clinical data and pharmacovigilance reporting have not demonstrated significant thrombogenic concerns with fibrinogen concentrate to date.^{20,34,35} However, fibrinogen concentrate administration in patients with hypofibrinogenemia and disseminated intravascular coagulation should be avoided and the focus placed on treatment of the underlying disease (ie, sepsis).

The advantage of factor concentrates is that the risk of viral infection is significantly reduced due to viral inactivation and removal that minimize the risk of transmitting viruses. Although fibrinogen concentrate is manufactured using human plasma from a large pool of donors, the production processes involved remove antibodies and antigens, largely mitigating the risk of immunologic and allergic reactions resulting from its administration, and provide a pure product without other cellular and protein contaminants.

Prothrombin Complex Concentrates

The PCCs are highly purified, lyophilized coagulation factors derived from plasma that include coagulation factors II, VII, IX, and X in concentrations that vary depending upon the lot and the manufacturer.³⁶ The PCCs initially available were developed for hemophilia management and included factor IX specific products such as Bebulin VH (Baxter Health Care Corp, Westlake Village, CA), Profilnine SD (Grifols, Barcelona, Spain), and FEIBA (Factor Eight Inhibitory Bypassing Activity) VH (Baxter Health Care Corp, Westlake Village, CA).³⁶ Bebulin and Profilnine contain low levels of factor VII, whereas FEIBA contains the activated form of VII (VIIa). Three-factor PCCs are still available in the United States and, in some countries, represent the only PCC available and, in the United States, used for off-label indications including bleeding in surgical patients.

However, four-factor PCCs are currently the PCC recommended for urgent vitamin K antagonist reversal (eg, warfarin) in all recently published guidelines. Four-factor PCCs contain the four critical vitamin K-dependent coagulation factors but also proteins C and S. Kcentra (CSL Behring, King of Prussia, PA) is the only four-component PCC available in the United States but is called Beriplex P/N (CSL Behring GmbH, Marburg, Germany) in other countries. Other four-component PCCs available in other countries include Octaplex (Octapharma, Vienna, Austria).

Despite the previous use of FFP for warfarin reversal, current guidelines recommend four-component PCC administration as a primary treatment for emergent reversal.³⁶⁻³⁹ There are multiple advantages of PCCs for urgent warfarin reversal when compared to FFP, including rapid acquisition, no need for crossmatching, rapid INR correction, small infusion volume (~20 mL per 500 IU), and purification by viral inactivation/nanofiltration to remove potential pathogenic viruses. Kcentra is FDA approved for vitamin K antagonist reversal in the setting of coagulopathy or significant bleeding in combination with vitamin K and can be used prior to urgent surgery in patients taking warfarin. Although a four-component PCC was only approved the United States in 2013, these factor concentrates have been available in mainland Europe and other countries and are increasingly administered to facilitate factor repletion in perioperative bleeding.

Use of Prothrombin Complex Concentrates for Perioperative Bleeding

Algorithms for managing perioperative bleeding especially using viscoelastic methods of point-of-care monitoring have routinely included PCC administration.^{34,36} However, in bleeding patients, a multimodal approach to managing bleeding includes fibrinogen repletion, correction of thrombocytopenia and/or platelet dysfunction following cardiopulmonary bypass, use of antifibrinolytic agents, and evaluating surgical sources of bleeding. Many of these topics will be covered in other chapters. However, PCCs therapy for factor depletion and as part of management strategies in treatment algorithms has become common. In patients with major hemorrhage, the critical role of massive transfusion protocols with blood product administration in addition to potential adjunct therapies, including PCCs, are important to consider. Coagulation management algorithms have been published using PCCs, and other potential coagulation factor concentrates in cardiac surgical patients and trauma.³⁴⁻³⁶ In many of these patients, tranexamic acid is also concomitantly administered along with fibrinogen repletion.

von Willebrand Factor

Human antihemophilic factor/von Willebrand factor complex is commercially available in the United States and is indicated for treatment and prevention of bleeding in adult patients with hemophilia A (classical hemophilia). This agent is also indicated in adult and pediatric patients with von Willebrand disease (VWD) for (1) treatment of spontaneous and trauma-induced bleeding episodes and (2) prevention of excessive bleeding during and after surgery. This applies to patients with severe VWD and patients with mild and moderate VWD for whom use of desmopressin is known or suspected to be inadequate. This agent is not indicated for the prophylaxis of spontaneous bleeding episodes.

This product is the first plasma-derived von Willebrand factor/factor VIII-containing concentrate that was pasteurized to reduce the risk of virus infection and approved for use in Germany in 1981, and it is now available in many countries worldwide for on-demand treatment and long-term prophylaxis in patients with VWD or hemophilia A (factor VIII deficiency). This agent is used off-label for bleeding with acquired VWD due to ventricular assist devices or aortic stenosis.³⁴

Hereditary Angioedema and C1 Esterase Inhibitor Concentrates

Hereditary angioedema (HAE) is a life-threatening disease resulting from the absence or genetic mutation of a complement component inhibitor called C1 esterase inhibitor (C1 INH). Although there are several variants of HAE, they share a final common pathway following tissue injury, intubation, or other inciting events, leading to unopposed activation of multiple inflammatory pathways and mediators including kallikrein and bradykinin that increase vascular permeability.⁴⁰ Angioedema produces increased permeability of submucosal or subcutaneous capillaries and postcapillary venules leading to plasma extravasation and subsequent swelling of critical airway structures and other systemic effects. The C1 INH concentrates have been used since 1974 in Europe and now are available in the United States for both preventing and terminating attacks. Two of these have now been licensed in the United States for use in HAE patients, one for prophylaxis (Cinryze [Shire, Lexington, MA]) and the other for treating acute abdominal and facial HAE attacks (Berinert-P [CSL Behring, King of Prussia, PA]). The use of C1 INH concentrates is critical in the perioperative management of HAE patients.⁴¹

Adverse Effects of Transfusions

The risks of allogeneic transfusion extend beyond viral transmission and include allergy, alloimmunization, anaphylaxis, bacterial sepsis, graft versus host disease, TRALI, TACO, renal failure, volume overload, and immunosuppression.⁴²⁻⁴⁴ Platelet transfusions also carry the added risk of bacterial contamination and they contain a high concentration of donor white blood cells. Transfusion of donor white blood cells has the potential to produce multiple adverse effects. Cytokines, such as interleukins 6 and 8, tissue necrosis factor alpha, and other inflammatory mediators are especially concentrated in platelet products and could contribute to adverse outcomes.

Transfusion as an Inflammatory Response

Transfusions of allogeneic blood is reported to have multiple immunomodulatory effects including immunosuppression; they contain bioactive substances that cause febrile reactions, and they release inflammatory mediators.⁴⁵ Inflammatory responses to cardiac surgery are affected by giving packed RBCs during surgery as displayed by neutrophil activation.⁴⁶ Neutrophils in allogeneic cellular blood components are associated with adverse effects in the recipient.⁴⁷ In cardiac surgical patients who are already immunosuppressed by surgical trauma, added inhibition of immunomodulation may have harmful effects.

Because of increasing awareness and identification of TRALI and decreases in the incidence of infectious and hemolytic complications of transfusions, TRALI is now a primary cause of transfusion-associated mortality reported to the FDA and has become a frequent cause of transfusion-related morbidity and mortality.⁴⁸ The TRALI can be confused with other transfusion and non-transfusion-related events such as anaphylaxis, hemolysis, circulatory overload, and cardiac failure and present with acute shock, florid pulmonary edema, and pulmonary hypertension.^{47,49} Because TRALI is a major cause of mortality resulting from transfusion, strategies have evolved to reduce its incidence and will be considered in more detail later.

Transfusion-Associated Circulatory Overload

The TACO is simply a volume overload state, where the rate of volume infusion of blood products is in excess of what the patient's cardiovascular status can handle. An example is the transfusion of 4 units of FFP to reverse warfarin in a patient with heart failure; in such a patient who can barely manage his or her own intravascular volume, he or she may well go on to develop orthopnea and paroxysmal nocturnal dyspnea following transfusion. The TACO is characterized by the acute onset of dyspnea and is typically associated with hypertension, tachypnea, and tachycardia—an exacerbation of heart failure as shown in **Table 28.3**. Sometimes, it can be difficult clinically to differentiate TRALI from TACO, but use of echocardiography, transthoracic or transesophageal, will reveal hypervolemia, ventricular dysfunction, and potentially reveal exacerbation of valvular dysfunction. In a TRALI patient, volume overload is not the cause of pulmonary edema, rather left ventricular size should be normal or low, and often, the right ventricle is dilated. Alternately, attesting for brain-type natriuretic peptide is another approach, and this should be greatly

elevated, usually several folds above a baseline of 100 to 200 in patients with TACO. The TACO incidence ranges from approximately 1% to 8% of transfusions. The TACO is increasingly reported as a common cause of morbidity and mortality associated with transfusion, especially with the use of FFP.

TABLE 28.3

Presentation of transfusion-associated circulatory overload

Dyspnea
Elevated jugular venous pressure
Hypertension or hypotension
Tachycardia
Rales on lung auscultation
Pulmonary edema
Increased brain natriuretic peptide
Echocardiography: hypervolemia, mitral regurgitation due to volume overload

Transfusion-Related Acute Lung Injury

The term *transfusion-related acute lung injury* was initially reported as the clinical presentation of hypoxia and bilateral noncardiogenic pulmonary edema within 6 hours of a transfusion.⁵⁰ Initially, this pathologic response was thought to be produced by donor immunoglobulin G antibodies against recipient neutrophils, called leukoagglutinins. The TRALI is secondary to TACO for transfusion-related deaths in the United States reported to the FDA.¹ The most widely accepted current concept is that TRALI results from neutrophil and/or endothelial activation via multiple mechanisms in the lung, resulting in pulmonary vascular injury and pulmonary edema.⁵⁰ Multiple pathogenic transfused factors are associated with TRALI and predisposing events that may prime the response as will be covered in more detail later and as summarized in [Figure 28.1](#).

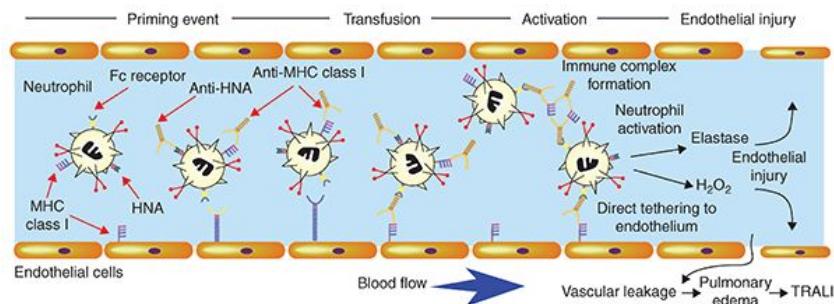


FIGURE 28.1 Transfusion-related acute lung injury (TRALI). Multiple priming events may or may not be required for TRALI but appear to be important factors in the inflammatory process that causes TRALI and may significantly potentiate the acute vasculitis that occurs. Transfusion of blood products from multiparous donors or other donors containing antibodies against white blood cell antigens that include human neutrophil antigen and major histocompatibility complex (MHC) class I can result in direct binding and activation of intravascular polymorphonuclear leukocytes. These antibodies may also directly bind and tether neutrophils to the endothelium independent of the adhesion molecules, selectin and integrin. The antigen-antibody binding also produces immune complexes of multiple white blood cell antigens that may also be recognized by the Fc receptors (tail receptors of antibodies) resulting in neutrophil activation. The activated neutrophils bind to the pulmonary vascular endothelium, and aggregated clumps of neutrophils may lodge in the pulmonary microcirculation. Activated neutrophils release multiple proinflammatory substances including proteolytic enzymes, oxygen free radicals, thromboxane, and other inflammatory mediators both locally at the site of vascular injury and systemically. This complex series of events results in damage to endothelial cells, vascular leakage, and pulmonary edema.

Clinical History of Transfusion-Related Acute Lung Injury

Initially, in the 1980s, this reaction was termed *pulmonary hypersensitivity reaction* and thought to be associated with leukocyte antibodies in the donor against the recipient, or in the recipient against the donor. In 1985, a series of 36 cases of TRALI were reported with acute respiratory failure characterized by hypoxemia and pulmonary edema occurring within 4 hours of transfusion. Granulocyte or lymphocytotoxic antibodies were detected in the donor of 89% of blood products. By 2006, more than 50% of transfusion-related fatalities reported to the FDA were due to TRALI. A National Heart, Lung, and Blood Institute working group defined TRALI as new acute lung injury (ALI) occurring within 6 hours of the end of transfusion of one or more plasma-containing blood products in patients without other risk factors for ALI. Patients with preexisting ALI and ALI occurring more than 6 hours after transfusion are excluded.

Clinical presentation of TRALI, in its severe form, is indistinguishable from adult respiratory distress syndrome and is characterized by acute-onset (within minutes to 6 hours after transfusion), bilateral pulmonary infiltrates and hypoxia without evidence of heart failure.^{42,51,52} Because reports use different definitions of TRALI, the information on incidence, outcome, and blood product association are variable. In German hemovigilance data of 44 cases of TRALI, the fatal 18% of cases were antibody-mediated from female donor blood. However, from multiple reports and European countries, the rates vary from approximately 1:11,363 (Finland) to 1:250,000. Five of the blood products implicated in TRALI, 49% were FFP, 29% RBCs, 13% platelet concentrates, 2% whole blood, 0% S/D plasma, and 7% mixed products. The American Red Cross–estimated risk of fatal TRALI per distributed component was 1:202,673 for plasma, 1:320,572 for apheresis platelets, and 1:2,527,437 for RBC units.⁵⁰ The TRALI mortality rates range from 5% to 35% in case series while leukocyte antibodies were identified in the implicated donor in 65% to 90% of TRALI cases.⁵⁰ **Table 28.4** lists clinical presentation of TRALI.

TABLE 28.4

Presentation of transfusion-related acute lung injury

Onset within 6 hours, usually more acute, following transfusion

Bilateral infiltrates seen on frontal chest radiograph

Hypoxemia/ratio of $\text{PaO}_2/\text{FiO}_2$ 300 mm Hg regardless of positive end-expiratory pressure level, or oxygen saturation of 90% on room air

Pulmonary artery occlusion ≤ 18 mm Hg when measured or lack of clinical evidence of left atrial hypertension (volume overload)

Pathophysiologic mechanisms: human neutrophil antigen (HNA) and human leukocyte antigen (HLA) class I and II antibodies, CD40 ligand (CD40L), biologically active lipids

Abbreviation: FiO_2 , fraction of inspired oxygen.

Multiple Factors Influence Transfusion-Related Acute Lung Injury

Although multiple factors may produce TRALI, priming events that occur before actual blood product administration may also be needed in what is termed the *two-hit model*.⁵⁰ First, an inciting inflammatory event may be required to activate and upregulate inflammatory cells and vascular endothelium (see “[Role of Neutrophils and Other Inflammatory Cells](#)” section), followed by a second, transfusion event that actually triggers an acute inflammatory response and injury. The initial priming event may be caused by lipids generated during prolonged storage of blood, recent infection including viral illnesses, and other events such as cardiopulmonary bypass that can trigger inflammatory responses and cytokine generation. Because neutrophils and endothelial cells are activated by multiple inflammatory events, there may be different thresholds for TRALI development in distinct settings from infection, lipid exposure, or extracorporeal circulation. Additional factors that likely contribute to the development of TRALI include complex factors such as antibody specificity and titer, antigen density, and the patient’s underlying condition.⁵⁰

Acute Pulmonary Edema and Management

The multiple signaling mechanisms and inflammatory mediators in TRALI promote priming and activation of a patient's granulocytes leading to their pulmonary sequestration and release of proteases, oxidants, and leukotrienes, which cause alveolar epithelial and microvascular endothelial damage resulting in increased permeability and the eventual development of noncardiogenic pulmonary edema. The two-hit model of TRALI is similar to pathophysiology of acute respiratory failure/syndrome. With TRALI, several reactive lipid-like substances that accumulate in RBCs or platelets during storage, referred to as biologic response modifiers, can act as the first pulmonary insult but are more likely the second. The first insult is generally a systemic inflammatory condition resulting from major surgery, sepsis, trauma, or pulmonary aspiration that causes activation of the pulmonary endothelium and priming of polymorphonuclear lymphocytes leading to their sequestration in the pulmonary vasculature. The second hit occurs when the primed polymorphonuclear lymphocytes are activated by the biologic response modifiers in the transfused component. Therapy for TRALI is supportive. Suspected cases of TRALI should be reported to the hospital transfusion service to assure a suitable investigation including testing of associated donors for antileukocyte and antiplatelet antibodies and typing recipients for HLA (ie, via leukocytes in a pretransfusion blood specimen or buccal swab technique). If donor leukocyte antibodies that react specifically to the patient's leukocytes are found, avoiding future transfusion of plasma-containing components from this donor is recommended. The patient, however, is not at an increased risk for future TRALI reactions with future transfusion.

A retrospective study of the incidence of acute pulmonary edema after transfusion in 8,902 ICU patients demonstrated 25 cases of TACO (incidence 1:356 units transfused), 7 cases of suspected TRALI (1:1,271 units transfused), and 14 cases of possible TRALI (1:534 units transfused).⁵³ Patients who developed suspected or possible TRALI received larger amounts of plasma, especially plasma from female donors. In addition, the mortality rate was 67% for suspected or possible TRALI, compared with 20% for TACO and 11% for matched controls.⁵³

Decreasing the Incidence of Transfusion-Related Acute Lung Injury

Because antibodies are present in most TRALI cases, especially severe and fatal cases, most policy changes made to mitigate TRALI have targeted antibody-mediated TRALI. Decreasing TRALI through changes in blood product policies is supported through biovigilance data and includes use of plasma from men only, resuspending pooled buffy coat platelets in plasma from men only, and screening female donors (either all or only those donors with a history of pregnancy, transfusion, or both) for leukocyte antibodies.⁵⁰ Recommendations for screening donors for leukocyte antibodies point to the need for screening patients at risk, including parous women and patients following transplantation and/or transfusion. Blood components with high plasma fractions that contain antibodies such as plasma, apheresis platelets, and whole blood should not be prepared from these donors.⁵⁰ The AABB also recommends implementing measures to minimize the preparation of high plasma-volume components from donors known to be leukocyte-immunized or at increased risk for immunization.

Plasma From Male Donors

Because TRALI is usually secondary to donor HLA or human neutrophil antigen antibodies, which are more common in females than males, the United Kingdom began using male donor plasma and resuspension of buffy coat-derived platelets in male-donated plasma. Since 2003, 80% to 90% of the United Kingdom FFP has been male-donated plasma. In 2004, the United Kingdom started using S/D plasma for plasma exchange procedures in thrombotic thrombocytopenic purpura patients. These changes resulted in a decrease in number of TRALI reports and deaths in the United Kingdom with a reduction from 1:65,000 to 1:317,000 ($P < .001$) for FFP, and 1:71,000 to 1:173,000 ($P = .068$) for platelets; the risks for RBCs (1:949,000) and cryoprecipitate (1:104,000) remained similar. Likewise, the American Red Cross reported a decrease in fatal and nonfatal TRALI cases after using only male-donated plasma in 2007 (from 26 cases in 2006 to 7 in 2008).⁵⁴

Transfusion-Related Acute Inflammatory Responses and Immunomodulation

Although TRALI is an important example of the complex inflammatory responses associated with transfusions, multiple blood products have the potential for proinflammatory responses including acute hypersensitivity responses and anaphylaxis that may not affect the lung. Inflammatory mediators including cytokines, tissue necrosis factor alpha, interleukin 6, and interleukin 8 are increased 100- to 1,000-fold over baseline in platelets and are also potentially elevated in other blood products.⁵⁵ Even though white cells are responsible for forming the high levels of inflammatory mediators including complement and cytokine factors, leukoreduction may be only partially effective in reducing the immunosuppressive effects of platelets.⁵⁶ Other mechanisms of immunosuppression not affected by leukoreduction may come into play.

Role of Neutrophils and Other Inflammatory Cells

Polymorphonuclear leukocytes are an important element of the innate immune response for host defense and are critical to controlling microbial pathogens after tissue injury following surgery or trauma. As part of all inflammatory responses, neutrophil-mediated events produce inflammatory responses that often become systemic producing widespread tissue damage and adverse sequelae. Neutrophils release multiple factors that kill both pathogens and surrounding tissue. Neutrophil activation is responsible for multiple inflammatory events, including reperfusion injury, a common issue following restoration of blood flow in occluded vessels. Following inflammatory insults, neutrophils and other inflammatory cells have important mechanisms of activation and recruitment and interact with vascular endothelial cells for further activation, localization, and extravasation/transmigration to areas of tissue injury or actual microbial invasion. Important inflammatory mediators and interactions with endothelial cells orchestrate these events by upregulating adhesion molecules after hypoxic challenge and production of inflammatory cytokines or pathogen metabolites that facilitate margination of leukocytes. Cytokines liberated as part of the inflammatory response induce changes in integrins and increase adhesion to the vascular wall followed by transmigration across the vessel wall. Chemotactic factors released locally further attract neutrophils to areas of primary tissue damage to kill invading organisms and remove necrotic tissue.

Summary

Blood and blood products are used extensively in the perioperative setting in surgical and trauma patients. Blood products and transfusions should be considered in the same manner that we consider use of other drug therapies by carefully weighing their risks and benefits. The complex environment in which we transfuse patients, the wide range of reasons to transfuse, and the different indications for blood product administration all further emphasize the importance of considering risk and benefit for each unique patient. The TACO and TRALI are major causes of morbidity and mortality associated with transfusions, and many therapeutic approaches have been adopted to decrease the risk. Both purified and recombinant therapeutic proteins will have an important role to play in the perioperative management of patients; despite their cost, these products do not need crossmatching and are likely to play an increasing role as alternatives to many blood products currently in use.

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Procoagulants

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Bleeding that occurs in surgical patients perioperatively or following trauma can arise from numerous causes beyond surgical factors that include activation of the coagulation, fibrinolytic, and inflammatory pathways, dilutional changes, and hypothermia.¹⁻³ Bleeding may be further exacerbated by the increasing use of multiple agents that affect coagulation, including oral and parenteral anticoagulants and platelet inhibitors. Hemostatic function and coagulation are complex and often altered in by multiple events that occur in the perioperative setting.¹⁻³ As a result, when patients bleed following surgery and trauma, multiple therapeutic approaches are often required in addition to blood transfusion, and procoagulants are now increasingly used to treat bleeding in the perioperative setting. This chapter focuses on the role of procoagulants used in a perioperative setting.

Antifibrinolytic Agents: Lysine Analogs

The two synthetic antifibrinolytic agents available are the lysine analogs epsilon aminocaproic acid (EACA) and tranexamic acid (TXA). These agents competitively inhibit activation of plasminogen to plasmin, an enzyme that degrades fibrin clots, fibrinogen, and other plasma proteins. Antifibrinolytic agents are not prothrombotic per se rather are clot stabilizers and prevent compensatory responses of inflammatory injury and clot lysis. The TXA also inhibits plasmin at higher doses,³ and most of the efficacy data are reported with TXA. The EACA does not consistently reduce transfusion requirements or surgical reexploration, especially in cardiac surgery, where these agents are best characterized.^{3,4} Multiple meta-analyses examining the use of antifibrinolytic agents consistently report a decrease in bleeding with use of these agents as measured by chest tube drainage, but data are limited for any conclusions about safety. The EACA has been removed from many European countries due to concerns about safety.³ Most studies reporting the use of antifibrinolytic agents are in cardiac surgical patients, but use in other patients, including orthopedic patients have also been reported. Aprotinin, a polypeptide protease inhibitor, is described later.

A meta-analysis of cardiac surgical patients compared aprotinin, TXA, and EACA.⁵ From 49 trials, 182 deaths among 7,439 participants were reported, and the relative risk for mortality with aprotinin versus placebo was 0.93. In the 19 trials that included TXA versus placebo, there were 24 deaths in 1,802 patients, yielding a relative risk of mortality of 0.55. To calculate direct estimates of death for aprotinin versus TXA, 13 trials with 107 deaths among 3,537 patients were evaluated. The relative risk was 1.43. Among 1,840 patients, the calculated estimates of mortality for aprotinin compared directly to EACA yielded a relative risk of 1.49. There was no evidence of an increased risk of myocardial infarction with aprotinin compared with TXA or EACA in either direct or indirect analyses, and all three drugs were effective in reducing the need for red blood cell transfusion.⁵ A more recent randomized study of 4,631 patients in coronary artery surgery compared TXA to placebo. The primary outcome was a composite of death and thrombotic complications within 30 days postoperatively. A primary outcome event occurred in 16.7% of TXA patients and in 18.1% of placebo ($P = .22$), and 4,331 allogeneic blood products were transfused in TXA patients compared to 7,994 in placebo ($P < .001$). A total of 1.4% of the TXA group required reoperation for bleeding compared to 2.8% of patients in placebo ($P = .001$), and seizures occurred in 0.7% and 0.1%, respectively ($P = .002$).⁶

One of the potential complications of TXA in cardiac surgery is seizures.³ The incidence of postoperative convulsive seizures at one institution was reported to increase from 1.3% to 3.8% following cardiac surgery, temporally coincident with high-dose TXA.⁷ In 24 patients who developed perioperative seizures, all had received high doses of TXA intraoperatively ranging from 61 to 259 mg/kg, had a mean age of 69.9 years, and 21 of 24 had undergone open chamber cardiac procedures.⁷ The ability of TXA to block γ -

aminobutyric acid receptors in the frontal cortex is a suspected mechanism, although other factors are likely involved that are specific to cardiac surgical patients.³

Antifibrinolytic agents also have been studied in other procedures, including orthopedic surgery, and all three agents reduce blood loss. Although most of the reported studies included small numbers of patients and lacked sufficient power, larger meta-analysis and more recent data suggest that these agents represent an important adjunct for reducing bleeding and the need for allogeneic transfusions. Multiple studies have examined the use of intravenous antifibrinolitics compared with placebo on transfusion requirement in orthopedic surgery and the safety of these agents, including venous thromboembolic risk.^{3,8} Zufferey et al⁸ evaluated 42 randomized trials in total hip and knee arthroplasty, spine fusion, musculoskeletal sepsis, or tumor surgery performed up to 2004. There were 22 trials with 1,238 participants for aprotinin, 20 trials with 1,096 participants for TXA, and 3 trials with 141 participants for EACA. Aprotinin and TXA both significantly reduced allogeneic blood transfusions compared to placebo. There was a dose-effect relationship with TXA, but EACA did not show any efficacy; antifibrinolytic use was not associated with an increased risk of venous thromboembolic events.

The TXA has also been studied in trauma patients and is being used more commonly for this application. Much of this increase in use is based on the Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage study, a study of the effects of early administration of TXA on death, vascular occlusive events, and blood transfusion in trauma patients conducted in 274 hospitals in 40 countries.⁹ A total of 20,211 adult trauma patients with (or at risk for) significant bleeding were randomly assigned within 8 hours of injury to receive either TXA (loading dose 1 g over 10 minutes and then infusion of 1 g over 8 hours) or placebo. The primary outcome was in-hospital death within 4 weeks of injury and was described as bleeding, vascular occlusion (myocardial infarction, stroke, and pulmonary embolism), multiorgan failure, head injury, or other causes. A total of 10,096 patients were allocated to TXA and 10,115 to placebo, of whom 10,060 and 10,067, respectively, were analyzed. All-cause mortality was significantly reduced with TXA (1,463 [14.5%] TXA group vs 1,613 [16.0%] placebo group; relative risk, 0.91; $P = .0035$). The risk of death due to bleeding was significantly reduced (489 [4.9%] TXA group vs 574 [5.7%] placebo group; relative risk, 0.85; $P = .0077$).

In the United States, clinicians often use EACA instead of TXA; however, most of the efficacy and safety data with antifibrinolytic use is TXA and not EACA. Furthermore, TXA is also approved in an oral form in the United States for the treatment of heavy menstrual bleeding. The recommended dose for women with normal renal function is two 650-mg tablets taken three times daily (3,900 mg per day) for a maximum of 5 days during monthly menstruation.

Antifibrinolytic Agents: Aprotinin

Aprotinin, a polypeptide serine protease inhibitor, inhibits plasmin and other serine proteases and has had a long history of use in different clinical applications. In cardiac surgery, multiple randomized, placebo-controlled trials reported aprotinin as effective in reducing bleeding and allogeneic transfusions.^{10,11} However, reports from observational databases^{12–15} and one randomized study¹⁶ questioned the safety of aprotinin. Following publication of the *Blood Conservation Using Antifibrinolitics: A Randomized Trial in a Cardiac Surgery Population* (BART) study,¹⁶ Bayer Pharmaceuticals removed the drug from the market in the United States, but it is currently available in Europe.¹⁷ A recent retrospective, single-center cohort study reports on 15,365 cardiac surgical patients, of which 1,017 received aprotinin and 14,358 received TXA. They noted aprotinin had a better risk-benefit profile than TXA in high-risk patients, but not in low- to moderate-risk patients and suggested its use in high-risk cases may be warranted.¹⁸

On September 21, 2011, Health Canada concluded that the benefits of aprotinin outweigh the risks when used as authorized by Health Canada. Aprotinin is authorized for patients undergoing coronary artery bypass graft surgery. The evidence evaluated did not suggest any increased risk of death associated with use of this agent. Health Canada's decision was based on a comprehensive review of the totality of evidence, which included an evaluation of BART study data, other clinical trial data, postmarket studies, and information from Bayer as well as an Expert Advisory Panel that was convened by Health Canada. One of the aspects

considered was that data suggesting an increased risk of death involved the use of aprotinin in complex, higher risk surgeries for which it is not authorized, such as valve replacement/repair. The precise nature of this risk remains unclear and merits further study. They also noted with respect to the BART study, Health Canada concluded that the study was not designed to reliably determine the risk of death (either within or outside of coronary artery bypass graft surgery) relative to the two drugs it was being compared against and that the increased number of deaths in aprotinin patients could have been due to chance.¹⁹

Protamine

Protamine is a polypeptide containing approximately 70% arginine residues and the only available agent to reverse unfractionated heparin. This basic protein inactivates the acidic heparin molecule via a simple acid–base interaction.²⁰ Protamine does not reverse low-molecular-weight heparin. Most patients receive too much protamine for anticoagulation reversal because plasma levels of heparin decrease over time, and most fixed-dose regimens for reversal give protamine based on the initial or total heparin dose and do not account for elimination.

Excess protamine should be avoided when reversing heparin as it can contribute to coagulopathy, as shown in [Figure 29.1](#).²¹ Protamine inhibits platelets and serine proteases involved in coagulation. Data suggests that maintaining heparin levels during cardiopulmonary bypass (CPB) and administering protamine based on the correct dose of circulating heparin reduces postoperative bleeding and the need for hemostatic factors.²² Part of this efficacy may be related to the finding that excess protamine prolongs the activated clotting time (ACT) and causes additional platelet dysfunction. When protamine is dosed based on the exact amount needed to reverse circulating heparin levels, it produces the lowest ACT values.²¹ Others have also reported lower protamine doses reduce bleeding and transfusion requirements.²³

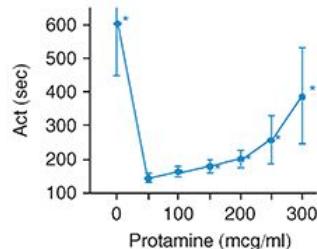


FIGURE 29.1 Excess protamine contribute to elevations in the activated clotting time (Act), at excesses of the exact dose required to reverse systemic anticoagulation. Thus, overdosage of protamine should be strictly avoided. *From Mochizuki T, Olson PJ, Szlam F, Ramsay JG, Levy JH. Protamine reversal of heparin affects platelet aggregation and activated clotting time after cardiopulmonary bypass. Anesth Analg. 1998;87(4):781-785.*

Heparin rebound can occur after initial reversal and is generally observed 2 to 3 hours after the first dose of protamine, when the patient is in the intensive care unit.²⁴ Heparin levels at this time may range from 0.1 to 0.3 IU/mL, equivalent to circulating levels of heparin, based on a 5 L blood volume, of 500 to 1,500 units. Protamine doses of 5 to 15 mg at this time may be effective at reversing heparin rebound rather than the dose of 50 mg commonly administered.²⁵ Studies have evaluated rotational thromboelastometry (ROTEM [Instrumentation Laboratory, Bedford, MA]) assay for determining the need for additional protamine administration and note that most patients do not need additional protamine administration within 30 minutes of initial administration. The ACT is not a sensitive indicator of low heparin concentrations because platelet counts and fibrinogen levels may also affect values.

Protamine can cause adverse reactions, including anaphylaxis, acute pulmonary vasoconstriction, right ventricular failure, and hypotension.²⁰ Patients at an increased risk for adverse reactions are sensitized, often from exposure to neutral protamine Hagedorn (NPH), which contains insulin and protamine.²⁰ In a study of 1,551 cardiac surgery patients, the incidence of protamine reactions was 1 out of 50 in insulin-dependent diabetics receiving NPH-insulin and 1 out of 501 among other patients.²⁶ A subsequent prospective study

found that reactions occurred in 0.6% (1 out of 160) of patients with NPH-insulin-dependent diabetes.²⁷ Other individuals reported at risk for protamine reactions include patients with vasectomy, multiple drug allergies, and prior protamine exposure.²⁰ Despite the potential for anaphylaxis, there are no currently available alternatives to protamine.

Desmopressin

Desmopressin (DDAVP) is the V2 analog of arginine vasopressin that stimulates the release of ultra-large von Willebrand factor (vWF) multimers from endothelial cells.²⁸ The vWF mediates platelet adherence to vascular subendothelium by functioning as a protein bridge between glycoprotein Ib receptors on platelets and subendothelial vascular basement membrane proteins. The DDAVP shortens the bleeding time of patients with mild forms of hemophilia A or von Willebrand disease (VWD).²⁹ The specific surgical patients who might benefit from the use of DDAVP are not clear. The DDAVP is administered intravenously at a dose of 0.3 mg/kg and should be given over 15 to 30 minutes to avoid hypotension.³⁰ Most studies have not confirmed the early reported efficacy during complex cardiac surgery. There have been 18 trials of DDAVP in 1,295 patients undergoing cardiac surgery that show a small effect on perioperative blood loss (median decrease, 115 mL).³¹⁻³² Because critically ill patients are often receiving vasopressin, which also has V2- and V1-mediated effects, there may not be a benefit to adding DDAVP to these patients.

The DDAVP is also used to treat VWD; there are multiple types of this deficiency, and therapy for each type varies. The DDAVP is most useful in type 3 (typically considered mild); in severe forms of types 1 and 2 VWD, DDAVP is not effective and vWF concentrates are available.³³ The VWD is the most frequent inherited bleeding disorder and is due to quantitative (types 1 and 3) or qualitative (type 2) defects of vWF.³³ The DDAVP is the treatment for type 1 VWD. In type 3 and in severe forms of types 1 and 2 VWD, DDAVP is not effective, and virally inactivated plasma vWF concentrates should be used in bleeding, surgery, and secondary long-term prophylaxis.³³

The DDAVP should be administered by slow intravenous infusion to avoid hypotension because it stimulates endothelial cells releasing vasoactive mediators in addition to vWF.³⁴⁻³⁵ Prior reports that DDAVP reduced blood loss and transfusion needs approximately 30% during complex cardiac surgery³⁶⁻³⁸ have not been confirmed.^{30,35} There have been 18 trials of DDAVP in 1,295 patients undergoing cardiac surgery that show a small effect on perioperative blood loss (median decrease, 115 mL). Although DDAVP may stimulate the release of vWF, its effect is likely minimal compared to multiple other factors involved in hemostasis. Also, DDAVP may be associated with other adverse effects as myocardial infarction was twofold higher compared to placebo with no improvement in clinical outcomes.⁶ However, in another review evaluating 16 trials of DDAVP in cardiac surgery and in other high-risk operations, the rate of thrombosis did not differ significantly between patients who received DDAVP and patients who received placebo (3.4% vs 2.7%).³⁹

Fibrinogen

Fibrinogen is a 340-kDa plasma glycoprotein synthesized in the liver and a critical component of effective clot formation.⁴⁰ It is the substrate of three important enzymes involved in clot formation: thrombin, factor XIIIa, and plasmin, as previously reviewed. The half-life is ~3.7 days. For clot formation, thrombin cleaves the fibrinogen molecule, producing a soluble fibrin monomer, which polymerizes to form a loose network in trapping red blood cells, and a clot begins to form. Cross-linking of the fibrin polymers, induced by factor XIIIa, is fundamental to the coagulation process, increasing the elasticity of the clot and its resistance to fibrinolysis. Fibrinogen also acts as the binding site (ligand) for glycoprotein IIb/IIIa receptors, found on the platelet surface, which are responsible for platelet aggregation. These platelets then become enmeshed within the fibrin strands, stabilizing the growing clot, and create the ability to cross-link and expand the clot and seal the bleeding site. During major hemorrhage, hemodilution after blood loss and subsequent volume replacement leads to reduced fibrinogen levels impairing fibrin polymerization and reduces clot stability. Thus, fibrinogen supplementation to restore plasma fibrinogen is key to normalizing clotting function.

Fibrinogen is a critical coagulation factor required for effective clot formation in surgical patients, and data supports hypofibrinogenemia as a predictor of perioperative bleeding.⁴¹⁻⁴³ Normal fibrinogen levels are

200 to 400 mg/dL, although, during the third trimester of pregnancy, fibrinogen levels are elevated to greater than 400 mg/dL. Although the optimal fibrinogen level needed in a bleeding patient is not known, bleeding increases for each 100 mg/dL decrease in fibrinogen level in parturients.⁴⁴ Low fibrinogen levels can predict bleeding after prolonged CPB.^{45,46} Treatment of fibrinogen deficiency is important for survival, and the amount of fibrinogen administered to trauma patients has been positively correlated with reductions in mortality.⁴⁰

In a bleeding patient, fibrinogen is an important factor to both measure and replete. Over the years, transfusion algorithms have targeted increasing levels of ~150 to 200 mg/dL (1.5-2.0 g/L), or potentially higher.⁴¹⁻⁴³ It is important to consider that low fibrinogen levels (<100 mg/dL) can increase laboratory measures of hemostasis, including prothrombin time (PT) and partial thromboplastin time, that may not be corrected with transfusing fresh frozen plasma. In this situation, cryoprecipitate or fibrinogen concentrates are a better option to restore adequate plasma levels and need to be considered when treating life-threatening bleeding. Fibrinogen can be repleted by cryoprecipitate; 1 unit per 10 kg increases fibrinogen by 50 to 70 mg/dL. In Europe, fibrinogen concentrates are available, and cryoprecipitate is not used. Fibrinogen concentrates are available (RiaSTAP [CSL Behring, King of Prussia, PA]), although approved for patients with congenital afibrinogenemia or hypofibrinogenemia.

Recombinant Coagulation Products and Factor Concentrates

Purified and recombinant proteins are becoming more readily available for managing bleeding, topical hemostasis, and for other therapeutic interventions.^{47,48} Factor concentrates are increasingly used in perioperative settings of bleeding and include fibrinogen, prothrombin complex concentrates, hemophilia factors VIII and IX, and XIII. Recombinant proteins can also be modified to alter specific characteristics that may be important in therapeutic effects or provide quantities that can be administered as a therapeutic agent to treat bleeding in hemophilia, VWD, and in patients with acquired antibodies/inhibitors, but also used off-label for refractory or life-threatening bleeding.

Recombinant Activated Factor VIIa

Recombinant activated factor VIIa (rFVIIa; NovoSeven [Novo Nordisk, Princeton, NJ]) is the activated form of factor VII (FVII) approved for treatment of bleeding episodes and perioperative management in patients with hemophilia A or B with inhibitors, congenital FVII deficiency, and Glanzmann thrombasthenia (the congenital absence of glycoprotein IIb/IIIa receptors) with refractoriness to platelet transfusions. Previously, rFVIIa has been extensively studied and continues to be used off-label as a prohemostatic agent for life-threatening hemorrhage.⁴⁹⁻⁵²

Recombinant FVIIa produces a prohemostatic effect by multiple mechanisms that include complexing with tissue factor (TF) expressed at the site of vascular injury to locally produce thrombin and amplify hemostatic activation.⁵⁰ Circulating FVIIa accounts for approximately 1% of circulating FVII and has no effect until bound with TF.⁵⁰ An increasing number of publications report the off-label use of rFVIIa in cardiac surgical patients. The therapeutic dose of rFVIIa in nonhemophilia patients has not been established.⁵¹ However, guidelines, as reported by Goodnough et al,⁵¹ for off-label use in patients with life-threatening hemorrhage have been reported.

Controlled clinical trials report the incidence of thrombotic complications among patients who received rFVIIa for bleeding and not hemophilia was relatively low, but due to the large number of patients reported, it was statistically significant compared to patients who received placebo.^{52,53} However, most case reports giving rFVIIa as rescue therapy include patients who have impaired coagulation, have received multiple transfusions, and are at a high risk for adverse events.

The complex role that both bleeding patients and transfusion therapy has in producing adverse outcomes is emerging in the scientific literature.⁵⁴⁻⁵⁶ A report using the U.S. Food and Drug Administration MedWatch database noted thromboembolic events in patients with diseases other than hemophilia in whom rFVIIa was used on an off-label basis and included 54% of the events as arterial thrombosis (eg, stroke or acute myocardial infarction).⁵⁷ Venous thromboembolism (mostly, venous thrombosis or pulmonary embolism)

occurred in 56% of patients. In 72% of the 50 reported deaths, thromboembolism was considered the probable cause. It is not clear to what extent the clinical conditions requiring the use of rFVIIa may have contributed to the risk of thrombosis.³¹ Other major issues about rFVIIa include costs and dosing. This drug has also seen widespread use in treating battlefield injuries ([Table 29.1](#)).

TABLE 29.1

Prohemostatic agents

Prohemostatic agent(s)	Specific drugs	Mechanism of action
Antifibrinolytics	Aprotinin, epsilon aminocaproic acid, tranexamic acid	Inhibition of plasminogen/plasmin-induced clot factor lysis
V2 agonists	Desmopressin (DDAVP)	Release of von Willebrand factor stored in the vascular endothelial storage sites (Weibel-Palade bodies)
Anticoagulant reversal agents/antidotes	Andexanet alfa, idarucizumab, protamine	Specific or nonspecific binding to anticoagulants to antagonize their effects
Factor concentrates	Fibrinogen, hemophilia factors (factor VIII, IX), factor XIII, prothrombin complex concentrates	Increase circulating levels of procoagulant proteins
Recombinant activated factor(s)	Activated factor VIIa	Specific single-protein activated factors that are considered bypassing agents to directly activate thrombin generation; currently approved for hemophilia with inhibitors, Glanzmann thrombasthenia, and used off-label for refractory bleeding
Topically applied hemostatic factors	Topical thrombin, microfibrillar collagen, fibrin glues	Applied directly to potential or active bleeding sites in an attempt to minimize or prevent potential bleeding; used extensively in surgical procedures and for microvascular bleeding

In the most recent cardiac surgical study,⁵⁸ patients bleeding postoperatively >200 mL per hour were randomized to placebo (n = 68), 40 µg/kg rFVIIa (n = 35), or 80 µg/kg rFVIIa (n = 69). The primary end points were the number of patients suffering critical serious adverse events. Secondary end points included rates of reoperation, blood loss, and transfusions. Although more adverse events occurred in the rFVIIa groups, they did not reach statistical significance (placebo, 7%; 40 µg/kg, 14%; P = .25; 80 µg/kg, 12%; P = .43). However, after randomization, significantly fewer patients in the rFVIIa group underwent a reoperation because of bleeding (P = .03) or needed allogeneic transfusions (P = .01).⁵⁸

One of the difficulties in using rFVIIa is that it can normalize elevated international normalized ratio (INR)/PT values without actually correcting the coagulation defect, especially in patients receiving warfarin and other vitamin K antagonists.⁵⁹ The use of currently approved component for prothrombin complex concentrates (PCCs) (Kcentra [CSL Behring, King of Prussia, PA]) is recommended in the guidelines and offers an important approach for the urgent reversal of warfarin.⁴⁸

Factor XIII

Plasma FXIII is a transglutaminase that cross-links fibrin, an important final step in clot formation that stabilizes the initial clot.⁶⁰ Congenital deficiency is rare but presents with spontaneous intracranial hemorrhages. In clinical studies, the addition of a plasma-derived FXIII (Fibrogammin [CSL Behring, King of Prussia, PA]) at the end of CPB with concurrent antifibrinolytic therapy reduced postoperative hemorrhage and transfusion requirement in cardiac surgery trial,⁶¹ and there was no reduction in bleeding in a larger randomized placebo-controlled clinical trial using a recombinant form of FXIII.⁶²

Prothrombin Complex Concentrates

The PCCs are concentrates of coagulation factors that include factors II, VII, IX, and X in variable concentrations.⁴⁸ Two agents (eg, Kcentra [CSL Behring, King of Prussia, PA] and Octaplex [Octapharma, Vienna, Austria]) are used worldwide for vitamin K antagonist-induced (ie, warfarin) reversal. Other PCCs available in the United States include FEIBA VH (Baxter, Vienna, Austria), Profilnine SD (Grifols, Barcelona, Spain), and Bebulin VH (Baxter, Vienna, Austria). They are approved for use in hemophilia and contain mainly factor IX.⁴⁸

The three-component and activated PCCs available in the United States are indicated for prevention/control of bleeding in patients with hemophilia B, although they are used extensively off-label for other indications. Only FEIBA contains FVII in an activated form, and Profilnine and Bebulin contain only low levels of FVII.⁴⁸ In general, it is considered preferable to give a PCC containing all four vitamin K-dependent coagulation factors and the natural anticoagulants antithrombin and activated protein C for warfarin reversal. Of note is that the PCCs are also increasingly being used off-label for managing bleeding in patients receiving the non–vitamin K oral anticoagulant direct factor Xa inhibitors (ie, rivaroxaban and apixaban).⁴⁸

Although clinicians continued to attempt warfarin reversal in the United States with fresh frozen plasma, in patients requiring urgent reversal for surgery or procedural interventions, PCCs are recommended.⁴⁸ These recommendations include reversal in patients with life-threatening bleeding and an increased INR when urgent reversal is required. Compared with fresh frozen plasma, PCCs provide quicker INR correction, have a lower infusion volume, and are more readily available without crossmatching without risk of volume overloading.^{63,64} The PCC consistently reduces the INR more rapidly than plasma with 55% of patients treated with four-factor PCC achieving a target INR of ≤ 1.3 versus 10% of patients in the plasma group at 30 minutes after the end of infusion.⁶⁴

Topical Hemostatic Agents

Topical hemostatic agents are used intraoperatively to promote hemostasis at the site of vascular injury and are classified based on their mechanism of action. They include physical and mechanical agents, caustic agents, biologic agents, physical agents, and physiologic agents.⁶⁵ The agent to use depends on the type of bleeding, the agent's specific mechanism of action, its interaction with the environment, and the underlying coagulopathy.⁶⁵ Absorbable agents include gelatin sponges (Gelfoam [Pfizer, New York, NY]), derived from purified pork skin gelatin that increases contact activation to help create topical clot. Surgicel or Oxycel is oxidized regenerated cellulose that works like Gelfoam (Pfizer, New York, NY). Avitene (Bard Davol, Warwick, RI) is microfibrillar collagen derived from bovine skin. Collagen sponges are available in different commercial forms and are derived from bovine Achilles tendon or bovine skin. Gelatin foam should not be used near nerves or in confined spaces but can be administered topically with thrombin. CoSeal (Baxter, Deerfield, IL) is used where swelling and expansion are not a concern. BioGlue (CryoLife, Kennesaw, GA) has been used in cardiac surgery, but it contains a glutaraldehyde component that cross-links proteins to fix tissues it is applied to.^{65–67}

Topically applied thrombin preparations are also used extensively. The first available thrombin was derived from bovine plasma (Thrombin JMI [Pfizer, New York, NY]). Although still available, bovine thrombin has been replaced in most clinical use by human thrombin due to its potential for antibovine thrombin antibody formation and immune-mediated coagulopathy.⁶⁶ Currently, there are two human thrombins available for clinical use, including plasma-derived thrombin (Evithrom [Ethicon, Summerville, NJ]) and recombinant human thrombin (RECOETHROM [Baxter, Deerfield, IL]).

Fibrin sealants, also referred to as **biologic glue** or **fibrin tissue adhesives**, are component products that combine thrombin (mostly human) and fibrinogen (usually plasma derived).⁶⁵ The first commercial fibrin sealant, Tisseel (Baxter, Deerfield, IL), was approved in 1989. Additional fibrin sealants are currently in use and include Crosseal (Ethicon, Summerville, NJ), E vicel (Ethicon, Summerville, NJ), and FloSeal (Baxter, Deerfield, IL). They are packaged with a dual-syringe delivery system that combines the components to form a fibrin clot.⁶⁷ The thrombin concentration determines the onset and the tensile strength fibrin seal.⁶⁷ Crosseal

(Ethicon, Summerville, NJ) contains human fibrinogen, human thrombin, and TXA. E vicel (Ethicon, Summerville, NJ) does not contain any fibrinolytic inhibitors. Several of these agents have been studied in cardiac surgical patients including FloSeal (Baxter, Deerfield, IL) and are the subject of a recent review.⁶⁷

Summary

The potential for bleeding in surgical patients represents an ongoing problem for clinicians. The increasing use of oral anticoagulation agents creates a need for multiple pharmacologic approaches as reviewed in the chapter on anticoagulation. Newer therapies, including purified factor concentrates such as the PCCs and potential recombinant therapies under development, will provide clinicians with the ability to administer key coagulation proteins to treat hemorrhage when standard therapies are ineffective, unavailable, or for other reasons that include no need for crossmatching. Therapy should be multimodal when managing perioperative hemostasis (**Figure 29.2**).⁶⁸ Understanding the complex physiology of hemostatic function is an important part of therapy, and procoagulation agents are part of a multimodal approach.

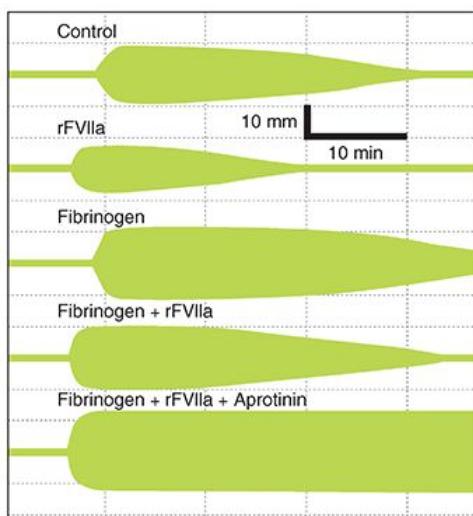


FIGURE 29.2 Thromboelastography recordings obtained with the ROTEM (Instrumentation Laboratory, Bedford, MA) device after the addition of recombinant activated factor VIIa (rFVIIa) and/or fibrinogen in the presence of tissue-type plasminogen activator in volunteer plasma. Tissue-type plasminogen activator was added to stimulate fibrinolysis, followed by rFVIIa in a final concentration 1.5 µg/mL and fibrinogen in a final concentration 100 mg/dL. The maximum clot firmness (the width of clot tracing) was only improved after the addition of fibrinogen. The onset of clotting was shorter after the addition of rFVIIa, but the extent of lysis (ie, decreased clot firmness) was increased in contrast to the samples with fibrinogen. Fibrinolysis was observed after the addition of rFVIIa and fibrinogen, and the clot structure was improved after the addition of an antifibrinolytic aprotinin. Reprinted with permission from Tanaka KA, Taketomi T, Szlam F, et al. Improved clot formation by combined administration of activated factor VII (NovoSeven) and fibrinogen (Haemocomplettan P). Anesth Analg. 2008;106(3):732-738. Copyright © 2008 International Anesthesia Research Society.

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Anticoagulants

Jerrold H. Levy

Anticoagulants are drugs that delay or prevent the clotting of blood. In a perioperative setting, patients receive anticoagulation for cardiovascular procedures, for thromboprophylaxis, or for cardiovascular disease and/or atrial fibrillation. The therapeutic potential of anticoagulation must be considered against risks for increased bleeding. Many agents are also used in the perioperative setting that may not be routinely monitored, including drugs such as low-molecular-weight heparin (LMWH), non–vitamin K oral anticoagulants that include direct thrombin inhibitors (dabigatran [Pradaxa] and factor Xa inhibitors rivaroxaban [Xarelto], apixaban [Eliquis], edoxaban [Savaysa], or P2Y₁₂ platelet inhibitors [clopidogrel and ticagrelor]). This chapter reviews the different anticoagulation agents, including antiplatelet agents, and considerations for their use in the perioperative use. The agents most commonly used will be considered in detail. Guidelines for management from different societies and journals are published and updated over time including American College of Chest Physicians and other societies that should be referred to for more detail.^{1–9}

Heparin

Unfractionated heparin (UFH) is an extract of porcine intestine or bovine lung, where heparin is stored in the mast cells. It is a mixture of highly sulfated glycosaminoglycans with molecular weights ranging from 3,000 to 30,000 Da that produce their anticoagulant effects by binding to antithrombin (AT) (previously known as antithrombin III), a circulating serine protease. Heparin acts as an anticoagulant by binding to AT, enhancing the rate of thrombin-AT complex formation by 1,000 to 10,000 times. Other factors in the clotting cascade, including not only factor Xa but also factors XII, XI, and IX, are also inhibited by AT.¹⁰ Anticoagulation thus depends on the presence of adequate amounts of circulating AT as shown in [Figure 30.1](#).

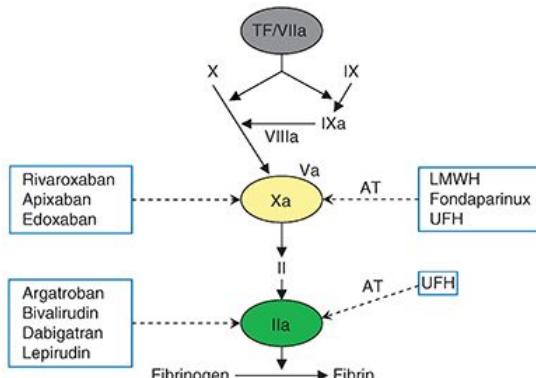


FIGURE 30.1 The major targets for anticoagulants in the coagulation pathway are directed against either factor Xa or thrombin (IIa). Unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) require circulating antithrombin (AT) as a cofactor, and only UFH will inhibit thrombin. Fondaparinux is a synthetic pentasaccharide and, like LMWH, indirectly inhibit factor Xa, requiring AT as a cofactor. The direct factor Xa inhibitors are AT-independent and include rivaroxaban, apixaban, and edoxaban. Both oral direct thrombin inhibitors (dabigatran) and intravenous agents directly inhibit thrombin. Vitamin K antagonists, such as warfarin, inhibit the activation of factors II, VII, IX, and X, as factors are made but are not activated by the posttranslational carboxylation that is inhibited (mechanism not shown). *Derived from Levy JH, Key NS, Azran MS. Novel oral anticoagulants: implications in the perioperative setting. Anesthesiology. 2010;113:726-745.*

Standardization of heparin potency is based on in vitro comparison with a known standard. A unit of heparin is defined as the volume of heparin-containing solution that will prevent 1 mL of citrated sheep blood from clotting for 1 hour after the addition of 0.2 mL of 1:100 calcium chloride. Heparin must contain at least 120 United States Pharmacopeia units per milliliter. Because the potency of different commercial preparations of heparin may vary greatly, the heparin dosing should always be prescribed in units, and most heparin is porcine in origin.

Pharmacokinetics

Heparin is a highly charged acidic molecule administered by intravenous (IV) or subcutaneous (SC) injection. The pharmacokinetics of heparin is based on measurements of its biologic activity using an anti-Xa assay. Over the range of heparin concentrations used clinically, the dose-response relationship is not linear for multiple reasons, including the need for AT to potentiate its effect, the effects of temperature, its highly charged nature that causes protein binding, and the variability of anticoagulation responses. The precise pathway of heparin elimination is uncertain, and the influence of renal and hepatic disease on its pharmacokinetics is less than with other anticoagulants. Heparin binds to many different proteins, which can affect its anticoagulant activity and contributes to heparin resistance.¹¹

Laboratory Evaluation of Coagulation

The anticoagulant response to heparin varies widely, especially in critically ill patients with alterations in AT and other plasma proteins. Different tests are used to monitor UFH and other anticoagulants as follows.²

Activated Partial Thromboplastin Time and Anti-Factor Xa

Heparin treatment is usually monitored to maintain the ratio of the activated partial thromboplastin time (aPTT) within a defined range of approximately 1.5 to 2.5 times normal values, typically 30 to 35 seconds. The aPTT has traditionally been the most commonly used test to monitor heparin, but certain factor deficiencies, including hemophilia and inhibitors of contact activation (eg, factor XII) can increase aPTT but may not increase the risk of bleeding. As a result, some hospital laboratories have changed to anti-Xa assays instead of aPTT monitoring because of the variability of responses, with low-dose regimens targeting levels of 0.3 to 0.5 unit/mL and high-dose regimens targeting levels 0.5 to 0.8 unit/mL. The aPTT is also used to measure the effects of direct thrombin inhibitors, including bivalirudin and argatroban, and is relatively sensitive to heparin levels up to approximately 1 unit/mL. At higher heparin concentrations, the activated clotting time (ACT) is used as follows.

Activated Clotting Time

The ACT is used primarily to determine anticoagulation for higher heparin concentrations, like those typically used during cardiopulmonary bypass. The ACT is performed by mixing whole blood with an activating substance that has a large surface area, such as celite (diatomaceous earth—silicon dioxide) or kaolin (clay—aluminum silicate). This is a contact activation through the classic intrinsic pathway where factor XII initiates activation of the clotting cascade. The activator speeds up the clotting time to normal values of approximately 100 to 150 seconds, depending on the device. Several commercially available timing systems used clinically to measure the ACT are based on detecting the onset of clot formation. Nevertheless, results between different commercial devices to measure the ACT may not be interchangeable, especially if the type of activator (celite or kaolin) is different.

Heparin effect and its antagonism by protamine are commonly monitored in patients undergoing cardiovascular procedures by measuring the ACT. Because the ACT is easy to use and reliable for high heparin concentrations (>1.0 unit/mL), it has become the mainstay of heparin anticoagulation monitoring in perioperative management and for cardiac catheterization. In addition to the presence of a heparin effect, the ACT may be influenced by hypothermia, thrombocytopenia, presence of contact activation inhibitors (aprotinin), and preexisting coagulation deficiencies (fibrinogen, factor XII, factor VII). With aprotinin

therapy, the recommendation is to use kaolin-ACT rather than a celite-ACT determination as kaolin binds to aprotinin to minimize its effect.

For cardiac surgery, a baseline value for the ACT is determined (1) before the IV administration of heparin, (2) 3 to 5 minutes after administration, and (3) at 30-minute intervals, thereafter. The ACT response to heparin is not linear for multiple reasons, including the need for AT for its effectiveness and because of several other factors that affect ACT. During cardiopulmonary bypass, the target ACT value is still controversial but often considered adequate if the ACT is longer than 350 seconds, although most cardiac surgical centers target an ACT of longer than 400 seconds. The need to measure ACT repeatedly is emphasized by the fourfold variation in heparin sensitivity between patients and the threefold variation in the rate at which heparin is metabolized. Furthermore, ACT values can be misleading during cardiopulmonary bypass with respect to heparin-induced anticoagulation because of the effects of hypothermia and hemodilution on the measurement system.¹²

Clinical Uses

Heparin is used extensively for multiple purposes, including the prevention and treatment of venous thrombosis and pulmonary embolism (PE), for acute coronary syndromes, and perioperative anticoagulation for extracorporeal circulation and hemodialysis. When administered intravenously, heparin has an immediate onset of action, whereas SC administration results in variable bioavailability with an onset of action in 1 to 2 hours.

Heparin-Induced Thrombocytopenia

Thrombocytopenia due to UFH is common and can begin within hours in patients exposed to heparin. However, a more severe and even life-threatening syndrome develops in 0.5% to 6.0% of patients, manifesting as severe thrombocytopenia (50% drop in platelet count or <100,000 cells/ μ L), that can be associated with thrombotic events (heparin-induced thrombocytopenia [HIT] with thrombosis). This severe response typically develops after 4 to 5 days of heparin therapy and is caused by heparin-dependent antibodies to platelet factor IV that trigger platelet aggregation and result in thrombocytopenia (see the more detailed discussion in physiology of hemostasis under [Chapter 27](#)).¹³

Allergic Reactions

Heparin can also cause allergic reactions, but these are rare and present in a manner typical of other hypersensitivity reactions. In patients who do experience immediate reactions, HIT should also be suspected due to the presence of preformed antibodies. The rapid IV infusion of large doses of heparin usually causes minimal hemodynamic changes.¹³

Reversal of Heparin-Induced Anticoagulation With Protamine

Protamine is one of the few agents available for reversing anticoagulation. Protamine is a strongly alkaline (nearly two-thirds of the amino acid composition is arginine), polycationic, low-molecular-weight protein found in salmon sperm. The positively charged alkaline protamine combines with the negatively charged acidic heparin to form a stable complex that is devoid of anticoagulant activity. These heparin-protamine complexes are removed by the reticuloendothelial system. Clearance of protamine by the reticuloendothelial system (within 20 minutes) is more rapid than heparin clearance and that may explain, in part, the phenomenon of heparin rebound. The dose of protamine required to antagonize heparin is typically 1 mg for every 100 units of circulating heparin activity. A more specific dose of protamine is calculated by heparin-protamine titration. Most clinicians give too much protamine because they reverse based on the total dose of heparin administered without accounting for heparin elimination prior to the administration of protamine. Heparin has a half-life of approximately 1 hour, so determinations of protamine dosing should include considerations of the circulating heparin level for reversal (see also “[Protamine](#)” in [Chapter 29](#)).

Low-Molecular-Weight Heparins

Enoxaparin and dalteparin are two commonly administered LMWHs derived from standard commercial-grade UFH by chemical depolymerization to yield fragments with a mean molecular weight of 4,000 to 5,000 Da. Depolymerization of heparin results in a change in its anticoagulant profile, pharmacokinetics, and effects on platelet function. Compared with heparin, which has an anti-Xa to anti-IIa activity of about 1:1, enoxaparin has a corresponding ratio that varies between 4:1 and 2:1.¹⁴ The pharmacokinetics of enoxaparin and dalteparin between patients are more consistent than heparin because these drugs bind less avidly to proteins than heparin. This contributes to better bioavailability at low doses. Although protection against venous thromboembolism (VTE) in high-risk medical and surgical patients is often thought to be better with LMWH than with heparin, LMWH's effect is considerably prolonged with renal failure and anticoagulants such as UFH should be used in this population. Therefore, care should be taken to delay surgery for 12 hours after the last dose of LMWH in patients with normal renal function and longer with renal dysfunction. Protamine does not neutralize LMWH.^{1-3,14}

Spinal and Epidural Hematomas

The risk of spontaneous hematoma formation may be increased in the presence of LMWH and indwelling epidural catheters for administration of postoperative analgesia and by concomitant use of other drugs that affect hemostasis (nonsteroidal antiinflammatory drugs, platelet inhibitors) and by traumatic or repeated attempts to accomplish entry into the epidural or subarachnoid space. This increased risk of hematoma formation is a consideration when selecting regional anesthesia in patients being treated with LMWH preparations. Recommendations for the management of patients for regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy are reported in the *American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines* (fourth edition).¹⁵

Fondaparinux

Fondaparinux is a synthetic anticoagulant composed of the five saccharide units that make up the active site of heparin that binds AT, such as LMWH, to inhibit factor Xa but has no direct activity against thrombin. Administered subcutaneously, fondaparinux is rapidly absorbed and has an elimination half-time of 15 hours, allowing for once daily administration. Metabolism does not occur, and the drug is eliminated by the kidneys and should not be used in patients with renal failure. Clinical uses of fondaparinux include prevention of deep vein thrombosis (DVT) and PE and as an alternative anticoagulant in patients with HIT. Because of its long duration of action, it is used primarily in patients with HIT or concerns about sensitization.¹⁶

Danaparoid

Danaparoid is a glycosaminoglycan that is derived from porcine intestinal mucosa and consists of a mixture mostly of dermatan sulfate and chondroitin sulfate. This low-molecular-weight heparinoid compound attenuates fibrin formation principally by binding AT. Elimination of danaparoid is predominately through the kidneys. Danaparoid is effective in decreasing the incidence of DVT following total hip arthroplasty and was used for the treatment of HIT. Although not currently available in the United States, it is used in other countries and being studied again for HIT management in clinical trials.

Prophylaxis Against Venous Thromboembolism

Surgical procedures have been associated with a 20-fold increase in risk for VTE, which is understandable, considering that the majority of surgical patients have one or more risk factors for developing VTE.² The incidence of DVT is 10% to 40% among general surgery patients and higher still in high-risk surgery patient populations (eg, orthopedic, thoracic, cardiac, and vascular surgery).^{2,3} Fortunately, thromboprophylaxis is known to effectively reduce VTE.¹⁻⁶

To prevent VTE, patients are treated with anticoagulants. Although SC heparin and LMWH are commonly used, multiple novel agents are also approved for different indications, including fondaparinux, rivaroxaban, and dabigatran with different indications depending on the country. Enoxaparin and dalteparin are commonly used LMWHs. Before the availability of LMWH, low-dose heparin, 5,000 units

subcutaneously every 8 to 12 hours, was a common regimen. In those with renal failure or renal dysfunction, heparin and warfarin are the only drugs minimally affected because of nonrenal clearance.

Among surgical patients, those undergoing total hip replacement are at a unique risk for developing DVT, and many of the studies for approval of new anticoagulants have focused on this group and other orthopedic patients. The risk of DVT is more protracted after hip surgery than after general surgery, when it usually develops during the first few postoperative days. The surgical technique for hip surgery, which kinks the femoral vein, seems to stimulate proximal DVT in the operated leg, whereas calf vein thrombosis is more likely to develop in either leg. Another effect unique to hip surgery is the impairment of venous hemodynamics, which may last several weeks in the operated leg. Indeed, there are significantly fewer venous thromboembolic complications in patients undergoing elective hip replacement when prophylaxis with LMWH is given for 1 month rather than only during the hospitalization. The VTE is also a common, life-threatening complication of major trauma. A PE has been observed to occur in 2% to 22% of patients with major trauma, and fatal PE is the third most common cause of death in patients who survive the first 24 hours.^{1–9,17}

Direct Thrombin Inhibitors: Parenteral Agents

An important class of anticoagulants that high-risk surgery patients at risk for or with HIT may receive are the direct thrombin inhibitors that include bivalirudin and argatroban (**Table 30.1**). Bivalirudin is also commonly used for cardiac interventional procedures and in an intensive care unit setting. The direct thrombin inhibitors also vary in their binding affinities for thrombin. Bivalirudin and other similar agents, including desirudin, bind in a bivalent manner to thrombin by interacting with both the catalytic site and fibrinogen-binding site. Bivalent direct thrombin inhibitors show higher affinity and specificity for thrombin compared with univalent direct thrombin inhibitors, which bind to the catalytic site only. Direct thrombin inhibitors vary substantially in their pharmacokinetic properties in terms of half-life and metabolism. The original direct thrombin inhibitors were modifications of the Leach protein hirudin and included desirudin and lepirudin, drugs that were the first agents of this class approved but no longer use or available.

TABLE 30.1

Direct thrombin inhibitors currently available

Drug	Dose	Clinical status	Indications current (future)	Recommended monitoring	Time to stop before surgery
Bivalirudin	Intravenous	Available in United States, Europe, and Canada	<ul style="list-style-type: none"> • PCI in patients with HIT • PTCA • Cardiac surgery (Canada) • Acute coronary syndromes (Europe) 	ACT	~4–6 hours
Argatroban	Intravenous	Available in United States and Europe	<ul style="list-style-type: none"> • Prophylaxis and treatment of thrombosis in HIT • PCI in patients with HIT 	aPTT ACT (PCI)	~4–6 hours
Desirudin	Subcutaneous	Not widely available	<ul style="list-style-type: none"> • Total hip arthroplasty • HIT 	aPTT	~24 hours
Dabigatran etexilate	Oral	Available in United States for stroke prevention for atrial fibrillation; approved in Europe and Canada for hip and knee arthroplasty	<ul style="list-style-type: none"> • Atrial fibrillation • DVT treatment and prevention • PE treatment and 	Not for routine: thrombin times — qualitative assay; diluted thrombin time and ecarin clotting time sensitive also for levels; aPTT to determine effect but not sensitive at low drug levels	~48 hours with normal renal function; ~72–96 hours or more if abnormal renal function. Drug effects can actually be measured as noted and potentially can be used to guide decision making.

			prevention after 5-10 days Rx with parenteral agent		
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Abbreviations: ACT, activated clotting time; aPTT, activated partial thromboplastin time; DVT, deep vein thrombosis; HIT, heparin-induced thrombocytopenia; PCI, percutaneous coronary intervention; PE, pulmonary embolism, PTCA, percutaneous transluminal coronary angioplasty; Rx, prescription.

Bivalirudin

Bivalirudin, a synthetic analogue of hirudin with a half-life of 25 minutes, has been widely studied in patients with and without acute coronary syndromes undergoing percutaneous coronary intervention (PCI). This agent is indicated for use in patients with unstable angina undergoing percutaneous transluminal coronary angioplasty; in patients with or at risk for HIT or HIT undergoing PCI; and with provisional use of glycoprotein (GP) IIb/IIIa inhibitors in patients undergoing PCI. Although it is a polypeptide, bivalirudin is considered a safe anticoagulant in patients with HIT. In patients with HIT antibodies undergoing cardiopulmonary bypass, bivalirudin provided safe and effective anticoagulation, with a 94% success rate for the procedures.¹⁸ Further, multiple studies have demonstrated its application as a heparin replacement in patients who are HIT-positive and require on or off-pump cardiac surgery, although this is an off-label use for the drug.¹⁸⁻²⁰

Argatroban

Argatroban is an injectable, synthetic, univalent direct thrombin inhibitor indicated for prophylaxis or treatment of thrombosis in patients with or at risk for HIT undergoing PCI. It has a relatively short half-life of 40 to 50 minutes, and anticoagulation returns to baseline when stopping it after approximately 4 hours.²¹ Patients with HIT are likely to have renal dysfunction, and most of the agents used for HIT are all primarily renally eliminated. Argatroban is hepatically eliminated; thus, no dose adjustments are required in patients with renal impairment. As lepirudin is renally eliminated and bivalirudin is partially (~20%) renally eliminated, their use may require dose adjustment in renally impaired patients to avoid accumulation. Antibodies to argatroban have not been detected after prolonged or repeated use due to its low molecular weight.²²

Lepirudin and Desirudin

Lepirudin and desirudin are synthetic analogues of hirudin, the direct thrombin inhibitor first isolated from leeches as *Hirudo medicinalis* is the name of the leech. These drugs were the first direct thrombin inhibitors that were originally approved for use in patients with HIT and associated thromboembolic disease. Lepirudin was initially reported for cardiac surgical patients; however, bleeding was a major problem due to its ability to irreversibly inhibit thrombin.^{16,22} Desirudin (another recombinant hirudin) was originally approved for the prevention of VTE after total hip or knee replacement surgery and was studied in cardiovascular patients undergoing percutaneous transluminal coronary angioplasty. With the advent of all of the newer direct thrombin inhibitors, and non-vitamin K oral anticoagulants, these drugs are either no longer available or used clinically.

Oral Anticoagulants

Vitamin K Antagonists—Warfarin

Oral anticoagulants are derivatives of 4-hydroxycoumarin (coumarin). Warfarin is the most frequently used anticoagulant because of its predictable onset and duration of action and its excellent bioavailability after oral administration ([Table 30.2](#)). Treatment usually begins with an oral warfarin dose of 5 to 10 mg, and the average maintenance dose is 5 mg; however, the dose varies widely among individuals due to pharmacogenetic differences. Warfarin has been the only oral agent available until the recent approval of new

agents that are described in the sections that follow. Disadvantages of warfarin include delayed onset of action, the need for regular laboratory monitoring, and difficulty in reversal should a surgical procedure create concern about bleeding.^{3,16}

TABLE 30.2

Current and emerging factor Xa inhibitors and vitamin K antagonist

Drug	Administration	Clinical status	Indications: current	Monitoring	Time to stop before elective surgery
Apixaban	Oral	Available most countries	Atrial fibrillation DVT treatment and prevention PE treatment and prevention	None	Low-risk bleeding: 1-2 days High-risk bleeding: 2-3 days
Danaparoid	Intravenous or subcutaneous	No longer available	Treatment of HIT; thromboprophylaxis in HIT patients	Calibrated plasma anti-Xa activity	No longer available
Low-molecular-weight heparin	Intravenous or subcutaneous	Available in most countries	Multiple: thromboprophylaxis Acute coronary syndromes	Plasma anti-Xa activity	At least 24-36 hours before Longer if renal dysfunction as elimination is prolonged; not reversible
Fondaparinux	Intravenous or subcutaneous	Available in most countries	Thromboprophylaxis and treatment of pulmonary embolism	Calibrated plasma anti-Xa activity	Long half-life of 17-21 hours; should be stopped at least 2 days; longer if renal dysfunction
Rivaroxaban	Oral	Available in Canada, Europe, and United States	Atrial fibrillation DVT treatment and prevention PE treatment and prevention With ASA to reduce CV events with CAD or PAD	None current	Low-risk bleeding: 1-2 days High-risk bleeding: 2-3 days
Heparin (UFH)	Intravenous or subcutaneous			aPTT, heparin levels (plasma anti-Xa)	4-6 hours before the procedure if possible but may need to continue for cardiovascular surgery; also reversible with protamine
Warfarin	Oral and intravenous		Anticoagulation for multiple reasons and treatment of thrombophilia	PT/INR	~5 days before procedure to allow INR <1.5 ? Bridging: depends on patient

Abbreviations: aPTT, activated partial thromboplastin time; CAD, coronary artery disease; CV, cardiovascular; DVT, deep vein thrombosis; HIT, heparin-induced thrombocytopenia; INR, international normalized ratio; PAD, peripheral arterial disease; PE, pulmonary embolism; PT, prothrombin time; UFH, unfractionated heparin.

Mechanism of Action

Warfarin inhibits vitamin K epoxide reductase that converts the vitamin K-dependent coagulation proteins (factors II [prothrombin], VII, IX, and X) to their active form, a posttranslational modification. The anticoagulant effect of oral or IV warfarin is delayed for 8 to 12 hours, reflecting the onset of inhibition of clotting factor synthesis and the elimination half-time of previously formed clotting factors that are not altered by the oral anticoagulant. Peak effects of warfarin do not occur for 36 to 72 hours.³

Pharmacokinetics

Warfarin is rapidly and completely absorbed, with peak concentrations occurring within 1 hour after ingestion. It is 97% bound to albumin, and this contributes to its negligible renal excretion and long elimination half-time of 24 to 36 hours after oral administration. Warfarin, however, does cross the placenta and produces exaggerated effects in the fetus, who has limited ability to synthesize clotting factors. Warfarin is metabolized to inactive metabolites that are conjugated with glucuronic acid and ultimately excreted in bile (enterohepatic circulation) and urine.

Laboratory Evaluation

Treatment with oral anticoagulants is best guided by measurement of the prothrombin time. The prothrombin time is particularly sensitive to three of the four vitamin K-dependent clotting factors (prothrombin and factors VII and X). Commercial prothrombin time reagents vary markedly in their responsiveness to warfarin-induced decreases in clotting factors. Therefore, prothrombin time results obtained with different reagents are not interchangeable between laboratories. This problem of variability in the responsiveness of prothrombin time reagents has been overcome by the introduction of a standardized system of reporting known as the international normalized ratio (INR). Each manufacturer assigns a specific value that indicates how a particular batch of tissue factor compares to an international reference tissue. The INR is the ratio of a patient's prothrombin time to a normal (control) sample, adjusted by the factor assigned by the manufacturer for the batch of factor being used in the assay. For most indications, a moderate anticoagulant effect with a targeted INR of 2.0 to 3.0 is appropriate, including prosthetic valve prophylaxis. An excessively prolonged prothrombin time is not readily shortened by omitting a dose because of the long elimination half-time of oral anticoagulants. Likewise, an inadequate therapeutic effect is not readily corrected by increasing the dose because of the delayed onset of therapeutic effect.

Unexpected fluctuations in the dose response to warfarin may reflect changes in diet, undisclosed drug use, poor patient compliance, surreptitious self-medication, or intermittent alcohol consumption. Concomitant medication with over-the-counter and prescription drugs can augment or inhibit the anticoagulant effect of coumarin drugs on hemostasis or interfere with platelet function. Patients receiving coumarin drugs are sensitive to fluctuating levels of dietary vitamin K, which is obtained predominantly from leafy green vegetables. The effect of coumarin can be potentiated in sick patients with inadequate vitamin K intake, particularly if they are treated with antibiotics and IV fluids without vitamin K supplementation. Preexisting liver disease and advanced age are associated with enhanced effects of oral anticoagulants.^{3,23}

Clinical Uses

Vitamin K antagonists (VKAs) are effective in the prevention of VTE, the prevention of systemic embolization and resultant stroke in patients with prosthetic heart valves or atrial fibrillation, and for treatment of patients with thrombophilia who are hypercoagulable. Because of the extensive new range of oral anticoagulants for perioperative VTE prophylaxis, these agents are used less and less for this indication.

Management Before Elective Surgery

In patients receiving a VKA, the INR should be checked preoperatively. Although minor surgical procedures can be safely performed in patients receiving oral anticoagulants, for major surgery, discontinuation of oral anticoagulants 1 to 3 days preoperatively is recommended to permit the prothrombin time to return to within 20% of its normal range. This approach, followed by reinstitution of the oral anticoagulant regimen 1 to 7 days postoperatively, is not accompanied by an increased incidence of thromboembolic complications in vulnerable patients. However, patients at high risk, such as those with prosthetic heart valves, may require bridging with UFH.³

Bleeding is the main complication of any anticoagulant therapy, including the VKAs. The risk of bleeding is influenced by the intensity of the anticoagulant therapy, the patient's underlying disorder, and the concomitant use of aspirin. Bleeding that occurs when the INR is less than 3.0 is frequently associated with an underlying cause (neoplasm, peptic ulcer). Anticoagulation drugs may increase the incidence of intracranial hemorrhage after a cerebrovascular accident. Compression neuropathy has been observed in treated patients after brachial artery puncture to obtain a sample for blood gas analysis. Treatment of bleeding depends on the severity and underlying patient and location. In emergency situations, oral or IV administration of vitamin K is used but will not immediately reverse the anticoagulant effect. If the immediate reversal is needed, for performance of high-risk surgical procedures such as craniotomy, administration of prothrombin complex concentrates (PCCs) is needed if available or other reversal strategies, as defined in Chapter 29.^{3,24} Guidelines for perioperative management are available.¹⁻⁷

Direct-Acting Non-vitamin K Oral Anticoagulants

For many years, warfarin has been the only oral anticoagulant available but has variabilities regarding dosing and effects and requires frequent monitoring and may take up to 5 days before therapeutic levels can be obtained. The newer therapeutic agents have a rapid onset with therapeutic anticoagulation within hours of administration and do not need routine monitoring. Dabigatran is an oral direct thrombin inhibitor, and rivaroxaban is a direct factor Xa inhibitor, similar to LMWH.¹⁶ Both of the newer agents require dose adjustments for renal failure and will be considered separately, along with agents still under investigation (see [Table 30.2](#)).^{9,16}

Direct Factor Xa Inhibitors

Rivaroxaban (Xarelto)

Rivaroxaban is an oral, direct factor Xa inhibitor with >10,000-fold greater selectivity for factor Xa than for other related serine proteases. In contrast to LMWH and similar agents, rivaroxaban does not require AT as a cofactor. Direct factor Xa inhibitors, including rivaroxaban, can inhibit free factor Xa, clot-bound factor Xa, and factor Xa bound to the prothrombinase complex, unlike indirect factor Xa inhibitors, such as fondaparinux, which are unable to inhibit factor Xa within the prothrombinase complex. Rivaroxaban is also a non-heparin-like molecule that may be suitable for the management of patients with HIT. Rivaroxaban is approved for prophylaxis of VTE during hospitalization and posthospital discharge to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation, treatment of DVT, PE, and reduction in the risk of recurrence of DVT and/or PE, prophylaxis of DVT in knee or hip replacement surgery, and in combination with aspirin, to reduce the risk of major cardiovascular events in patients with chronic coronary artery disease or peripheral artery disease.^{9,16}

When used with neuraxial anesthesia, an epidural catheter should not be removed earlier than 18 hours after the last administration of rivaroxaban, and the next rivaroxaban dose should be administered no earlier than 6 hours after the removal of the catheter and as noted in the manufacturer's package insert and in American Society of Regional Anesthesia and Pain Medicine guidelines.

Apixaban (Eliquis)

Apixaban is another oral, direct factor Xa inhibitor administered twice daily. Apixaban is approved to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation; in patients with prophylaxis of DVT, which may lead to PE; in patients who have undergone hip or knee replacement surgery; and for the treatment of DVT and PE and to reduce the risk of recurrent DVT and PE following initial therapy.

When used with neuraxial anesthesia, indwelling epidural or intrathecal catheters should not be removed earlier than 24 hours after the last administration of apixaban, and the next dose of apixaban should not be administered earlier than 5 hours after the removal of the catheter as noted in the manufacturer's package insert and 4 to 6 hours in American Society of Regional Anesthesia and Pain Medicine guidelines.

Edoxaban (Savaysa)

Edoxaban is also an oral, direct factor Xa inhibitor administered once daily. Current indications are to reduce the risk of stroke with nonvalvular atrial fibrillation and for the treatment of deep DVT and PE following 5 to 10 days of initial therapy with a parenteral anticoagulant.

Direct Thrombin Inhibitors

Ximelagatran

Ximelagatran is an oral, direct thrombin inhibitor that was approved in Europe for the VTE prophylaxis but later withdrawn from the market in 2006 due to concerns over potential liver toxicity. However, ximelagatran provided proof of principle that oral agents that act via direct inhibition of thrombin were an effective mode of action for new anticoagulants.¹⁶

Dabigatran Etxilate (Pradaxa)

Dabigatran etexilate is an oral, direct thrombin inhibitor approved to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation, for the treatment of DVT and PE in patients who have been treated with a parenteral anticoagulant for 5 to 10 days, and to reduce the risk of recurrence of DVT and PE in patients who have been previously treated. Dabigatran's effects can be best measured by thrombin times, diluted thrombin times, and ecarin clotting times, although aPTT values can be used for screening.²⁵ Administration of the first dose should occur a minimum of 2 hours after the catheter is removed, and patients should be observed for neurologic signs and symptoms.^{9,16} Dosing should also be adjusted for patients with renal dysfunction.

Perioperative Management of the Direct-Acting Non–vitamin K Oral Anticoagulants

The newer therapeutic agents have a rapid onset with therapeutic anticoagulation within hours of administration and do not need routine monitoring. Dabigatran is an oral direct thrombin inhibitor, and rivaroxaban is a direct factor Xa inhibitor, similar to LMWH.¹⁶ Both of the newer agents require dose adjustments for renal failure.¹⁶ One of the new challenges with use of these agents is how to effectively manage patients perioperatively. In the United States, PCCs are recommended in guidelines for immediate INR reversal along with vitamin K administration.²⁴ Vitamin K, however, without PCCs takes days to reverse and synthesize new active coagulation factors. Although fresh frozen plasma (FFP) is still often used, it is associated with transfusion risk, volume overload, and FFP does not restore the INR to <1.3 but usually to approximately 1.4 to 1.6, which is the baseline INR for FFP.²⁴ The PCCs are also used increasingly off-label for managing bleeding in patients receiving the Xa inhibitors including apixaban, edoxaban, and rivaroxaban. Although andexanet alfa is currently approved in the United States for life-threatening bleeding, it has not been studied in surgical patients, has a short duration of effect of several hours, and is expensive, costing \$25,000 per gram.²⁶ For the reversal of dabigatran, there is a specific antidote called idarucizumab, a monoclonal antibody fragment that has been extensively studied in surgical patients; however, dabigatran is not widely used in the United States.²⁶

Although routine monitoring of the new anticoagulants is not standard, if needed, they are best evaluated with specialized tests. For dabigatran, thrombin clotting time, ecarin clotting time, and aPTT can measure its effects.²⁶ Prothrombin time (INR) is not recommended. The aPTT, a standard test, can provide a useful qualitative assessment of anticoagulant activity but is less sensitive at supratherapeutic dabigatran levels, and limited data exists for ACT. Overall, the aPTT and thrombin clotting time are the most accessible qualitative methods for determining the presence or absence of anticoagulant effect.²⁶ For rivaroxaban, prolongation of most standard hemostatic tests are too variable and specialized tests evaluating anti-Xa are required.²⁶

Two important recent studies have been published to guide management. In the BRIDGE study, Douketis et al. randomized atrial fibrillation patients to bridging anticoagulation therapy with LMWH (dalteparin) or placebo from 3 days before the procedure until 24 hours before the procedure and then for 5 to 10 days after the procedure.²⁷ Warfarin treatment was stopped 5 days before the procedure and was resumed within 24 hours after the procedure and included 1,884 patients. Arterial thromboembolism was 0.4% in the no-bridging group and 0.3% in the bridging group ($P = .01$ for noninferiority); however, major bleeding was 1.3% in the no-bridging group and 3.2% in the bridging group ($P = .005$ for superiority).²⁷

Another important report is the Perioperative Anticoagulation Use for Surgery Evaluation cohort study that included 3,007 nonvalvular atrial fibrillation patients who were long-term users of apixaban, dabigatran, or rivaroxaban, scheduled for an elective surgery or procedure. The protocol was designed with a strategy based on direct-acting non–vitamin K oral anticoagulant pharmacokinetic properties, procedure-associated bleeding risk, and creatinine clearance levels. The direct-acting non–vitamin K oral anticoagulants were stopped 1 day before a low-bleeding risk procedure and 2 days before a high-bleeding risk procedure, and resumed 1 day postoperatively after a low-bleeding risk procedure and 2 to 3 days after a high-bleeding risk procedure. Major bleeding and arterial thromboembolic events were determined, and the minimal residual anticoagulant level was considered to be <50 ng/mL) at the time of the procedure. There were ~42% apixaban, ~22% dabigatran, and 36% rivaroxaban-treated patients of which 33.5% were undergoing a high-bleeding risk procedure. The 30-day postoperative rate of major bleeding was 1.35% in the apixaban, 0.90%

in the dabigatran, and 1.85% in the rivaroxaban cohorts. Arterial thromboembolism was low with 0.16% in the apixaban, 0.60% in the dabigatran, and 0.37% in the rivaroxaban cohorts. In patients with a high-bleeding risk procedure, the rates of major bleeding were ~3% per group.²⁵

In summary, for those who require emergency urgent surgery, warfarin can be rapidly reversed with PCCs, and dabigatran with idarucizumab and has been studied in this indication. Andexanet has only been studied for life-threatening bleeding and not in all patients and is costly. For elective surgery, growing data as reviewed suggests bridging it is not required, especially in patients with atrial fibrillation, but patient should be considered on a case-to-case basis, and risk versus benefit should be considered in logical decision making.

Platelet Inhibitors

Aspirin

Antiplatelet agents are the mainstay therapy for patients with atherosclerotic vascular disease and coronary artery disease, therapy consistent with the role of platelets in atherosclerosis.²⁸ Treatment with aspirin reduces the incidence of occlusive arterial vascular events. Aspirin irreversibly acetylates cyclooxygenase and thereby prevents the formation of thromboxane A₂. Despite rapid clearance from the body, the effects of aspirin on platelets are irreversible and last for the life of the platelet, 7 to 10 days. Guidelines suggest in patients who require temporary interruption of aspirin- or clopidogrel-containing drugs before surgery or a procedure, stopping this treatment 7 to 10 days before the procedure is recommended over stopping this treatment closer to surgery. In patients who have had temporary interruption of aspirin therapy because of surgery or a procedure, resuming aspirin approximately 24 hours (or the next morning) after surgery when there is adequate hemostasis is recommended instead of resuming aspirin closer to surgery.

Thienopyridines: Clopidogrel, Prasugrel, and Ticagrelor

Currently approved thienopyridines include clopidogrel (Plavix), prasugrel (Effient), and ticagrelor. The first two agents are prodrugs requiring *in vivo* metabolism each to an active metabolite, as shown in [Table 30.3](#). Ticlopidine is now rarely used clinically and will not be considered. Thienopyridines irreversibly bind to P2Y₁₂ receptors, thereby blocking adenosine diphosphate (ADP) binding. This P2Y₁₂ receptor antagonism inhibits ADP-mediated platelet activation and aggregation due to the critical role ADP plays in platelet function. When ADP is secreted from internal stores, it amplifies platelet responses induced by other platelet agonists to increase activation, an internal to external signaling mechanism.²⁹ The ADP-induced signal is again mediated by P2Y receptors, which are G-coupled 7-membrane-spanning proteins that are present in many different cells.^{28–30} There are multiple other P2Y receptor subgroups, but the G_i-coupled P2Y₁₂ receptor mediates inhibition of adenylyl cyclase and amplifies the platelet aggregation response.

TABLE 30.3

Current oral antiplatelet agents

	Clopidogrel	Prasugrel	Ticagrelor	Aspirin
Drug class	Thienopyridine	Thienopyridine	Thienopyridine	Acetylsalicylate
Mechanism of action	Selective, irreversible binding to and inhibition of P2Y ₁₂ receptor on platelets	Selective, irreversible binding to and inhibition of P2Y ₁₂ receptor on platelets	Selective, reversible binding to and inhibition of P2Y ₁₂ receptor on platelets	Cyclooxygenase inhibition
Comments	Prodrug, metabolized to active form by two different metabolic steps; resistance due to metabolism	Prodrug, metabolized to active form one metabolic step; more potent and resistance rare	Direct-acting agent	Active drug but resistance can occur; likely due to absorption and other factors

Cangrelor

Cangrelor is another ATP analogue that blocks P2Y₁₂ receptor-mediated platelet activation and is the only IV P2Y₁₂ inhibitor available for clinical use. Cangrelor has a rapid onset and offset, a 3- to 6-minute plasma half-life, and platelet function recovery within 30 to 60 minutes after stopping the infusion. Cangrelor is

approved for clinical use by the U.S. Food and Drug Administration as an adjunct to PCI to reduce the risk of myocardial infarction, repeat coronary revascularization, and stent thrombosis in patients who have not been treated with a P2Y₁₂ platelet inhibitor and are not being given a GP IIb/IIIa inhibitor. As a short-acting platelet inhibitor, cangrelor has been studied as a potential agent to maintain therapeutic antiplatelet effects for patients receiving clopidogrel or ticagrelor up to the time of their surgical procedure, when their oral agents cannot be stopped the standard recommended times of 5 days.

Dual antiplatelet therapy—a thienopyridine (ADP P2Y₁₂ receptor antagonist) coadministered with aspirin—is commonly used for improving clinical outcomes in patients with acute coronary syndrome and undergoing percutaneous intervention. New agents include prasugrel and ticagrelor. Ticagrelor is a reversible, direct-acting P2Y₁₂ receptor antagonist. The P2Y₁₂ is a G_i-coupled platelet receptor for ADP that plays a central role in platelet function. Drugs that inhibit P2Y₁₂ are potent antithrombotic drugs. Clopidogrel is the most widely used agent, but resistance, as defined as its inability to inhibit adequately P2Y₁₂-dependent platelet function, occurs in 20% to 30% of patients. Prasugrel and ticagrelor appear to be more effective than clopidogrel in preventing thrombosis, although they increase the incidence of major bleeding, a problem with the efficacy of all anticoagulants.

Current recommendations are to discontinue thienopyridines 5 to 7 days before elective surgery and to avoid regional anesthesia until the effects of these drugs have dissipated. Guidelines for the management of patients with coronary stents on antiplatelet agents have been proposed and are often elaborate ([Figure 30.2](#)). The guidelines take into consideration the type of coronary stent used, and the interval since the stent was placed as well as the urgency of need for surgery in decision making.

Dipyridamole

Dipyridamole is an agent that increases cyclic adenosine monophosphate in platelets to inhibit their function. This agent was also used for cardiac stress testing because of its coronary vasodilatory effects (dipyridamole-thallium stress test). Currently, it is most frequently administered in combination with aspirin to prevent stroke in patients who cannot take a thienopyridine. It can increase bleeding and should be stopped preoperatively, but the aspirin component has a longer half-life than dipyridamole.

Dextran

Dextran 70 (70,000 Da) binds to platelets and inhibits their function. This agent was used clinically to reduce thrombosis after carotid surgery and a few other indications but is now rarely used for this indication.

Platelet Glycoprotein IIb/IIIa Antagonists

An important advance in managing ischemic cardiovascular disease was the development of platelet GP IIb/IIIa receptor inhibitors, although these agents are now often replaced with newer therapies. The IIb/IIIa receptor antagonists (abciximab, tirofiban, eptifibatide) either bind or competitively inhibit the corresponding fibrinogen receptor that is important for platelet aggregation. These drugs block fibrinogen binding to platelet GP IIb/IIIa receptors that are a common pathway of platelet aggregation. In multiple clinical trials, they have provided proof of concept on the critical role that platelet inhibition has in reducing ischemic events associated with acute coronary syndrome and PCIs. In recent years, thienopyridines and direct thrombin inhibitor (bivalirudin) in addition to PCIs, including stenting have had a significant impact; nonetheless, inhibiting platelet function has been critical to prevent platelet responses to vascular injury and clot formation. These agents prevent thrombus formation initiated by platelets in the pathogenesis of acute coronary syndrome (unstable angina, myocardial infarction), angioplasty failure, and stent thrombosis but are decreasingly used with oral P2Y₁₂ therapies in the advent of cangrelor.^{[30](#) [31](#)}

Various antagonists of GP IIb/IIIa are available. The first of these agents, the monoclonal antibody abciximab (ReoPro), was approved for use in PCI. Tirofiban (Aggrastat), a nonpeptide, for treatment of acute coronary syndromes (unstable angina or non–Q-wave myocardial infarction) and eptifibatide (Integrilin), a peptide, for use both in PCI and acute coronary syndromes. New nonpeptide oral antagonists of GP IIb/IIIa intended for long-term use are in various stages of clinical development and may find application in a broad

spectrum of atherothrombotic disease. Although GP IIb/IIIa antagonists are indicated for the acute coronary syndrome and in patients undergoing interventional cardiology procedures, thienopyridines have largely replaced these agents due to cost and increasing clinical data favoring the thienopyridines. Abciximab has the longest half-life of all these agents as a monoclonal antibody, whereas the other agents have shorter half-lives. All of three agents can cause thrombocytopenia.³¹

Perioperative Management of Patients on Platelet Inhibitors

Perioperative management of patients on various platelet inhibitors is complex and requires careful coordinated care with multiple specialties. The risks and benefits of discontinuing antiplatelet therapy must be carefully considered for each individual patient, especially prior to elective surgery. Recent guidelines are listed in [Figures 30.2](#) and [30.3](#).

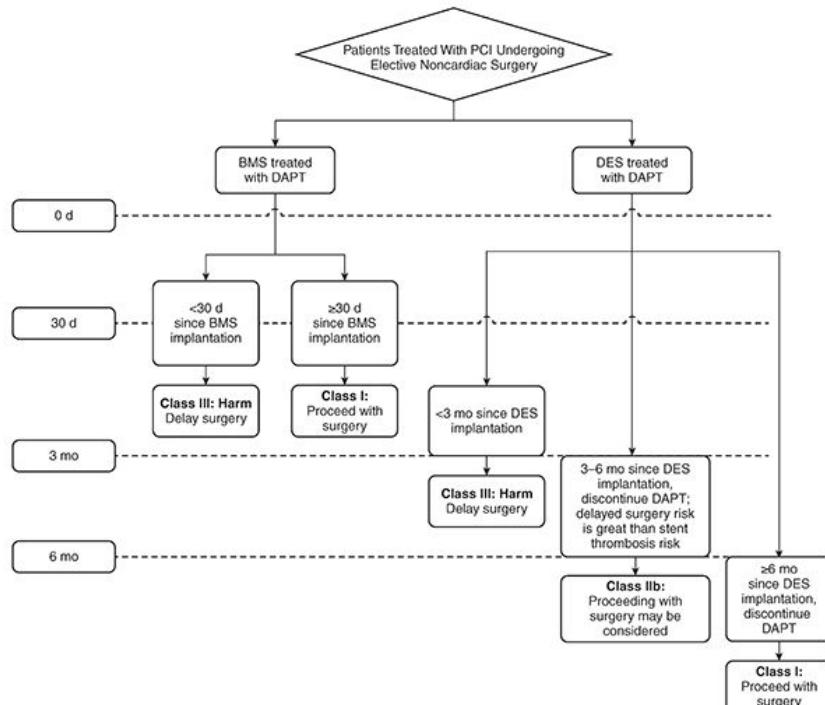


FIGURE 30.2 Treatment algorithm for the timing of elective noncardiac surgery in patients with coronary stents. Abbreviations: BMS, bare metal stent; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; PCI, percutaneous coronary intervention. Reprinted from Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2016;68(10):1082-1115. Copyright © 2016 by the American College of Cardiology Foundation and the American Heart Association, Inc. With permission.

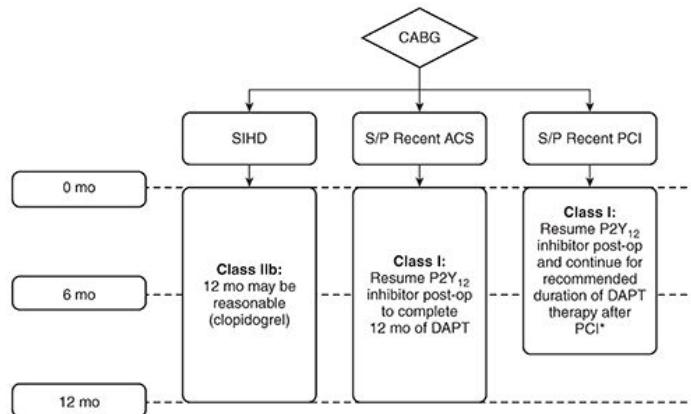


FIGURE 30.3 Treatment algorithm for management and duration of P2Y₁₂ inhibitor therapy in patients undergoing coronary artery bypass grafting. Aspirin therapy is almost always continued indefinitely in patients with coronary artery disease. Duration of dual antiplatelet therapy (DAPT) can vary from as little as 4 weeks to >12 months, depending on the clinical setting and bleeding risk. Abbreviations: ACS, acute coronary syndrome; CABG, coronary artery bypass graft surgery; PCI, percutaneous coronary intervention; post-op, postoperatively; SIHD, stable ischemic heart disease; S/P, status post. Reprinted from Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2016;68(10):1082-1115. Copyright © 2016 by the American College of Cardiology Foundation and the American Heart Association, Inc. With permission.

Thrombolytic Drugs

Pharmacologic thrombolysis is produced by drugs that act as plasminogen activators to convert the endogenous proenzyme plasminogen to the fibrinolytic enzyme plasmin that lyses clot and other proteins. The goal of thrombolytic therapy is to restore circulation through a previously occluded artery or vein, most often a coronary artery. Fibrinolytic therapy was used previously in the treatment of acute coronary syndrome, but current American College of Cardiology and American Heart Association published evidence-based guidelines for the management of patients depend on whether a conservative (ie, noninvasive) approach or an invasive strategy (ie, PCI with possible angioplasty or coronary artery bypass graft surgery) is possible, specifically whether cardiac catheterization is available. Tissue plasminogen activator (tPA) is indicated for the treatment of acute ischemic stroke, acute myocardial infarction to reduce mortality and incidence of heart failure with the limitation the risk of stroke may be greater than the benefit in patients at low risk for death from cardiac causes, and acute massive PE for lysis.

Acute interventions with fibrinolytic agents can be lifesaving in patients with pulmonary emboli,³² ischemic stroke (eg, middle cerebral arterial occlusion),^{6,33} and in patients suffering acute myocardial infarction without immediate access to PCIs.³⁴ Bleeding complications (5%-30%) may occur whether fibrinolytics are injected systemically or directly into the affected arterial lesion.³⁵ Currently available fibrinolytics include streptokinase, urokinase, and tPA. These agents activate plasminogen to plasmin, the major enzyme responsible for clot breakdown. Plasmin is a serine protease that degrades fibrin(ogen) and multiple hemostatic factors and proteins. In clinical practice, tPA is most commonly used because of its localized catalytic effect on plasminogen activation in the presence of fibrin.^{36,37} Blood flow to the thrombus is vital for the delivery of tPA, and thus, localized activation of fibrinolysis via catheter-directed drug delivery is theoretically more favorable than systemic administration.

Thrombolytic agents have an associated risk of bleeding (particularly intracranial hemorrhage), and hemorrhagic complications occur more often in trauma, surgery, or following invasive diagnostic procedures. Intracranial hemorrhage occurs in 1.7% to 8.0% of treated patients.³⁷ Following lytic therapy, hemorrhagic

transformation of ischemic infarcts can occur. The recommended treatment of intracranial or serious systemic bleeding after thrombolytic therapy is administration of cryoprecipitate and platelets, although evidence-based guidelines for such an approach are lacking.³⁷ Angioedema occurs in 1% to 5% of patients receiving recombinant tPA, and the use of angiotensin-converting enzyme inhibitors is strongly associated with this complication.³⁷

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Physiology and Management of Massive Transfusion

Jerrold H. Levy

Hemorrhage due to uncontrolled bleeding is a clinical problem commonly faced by clinicians managing traumatic injury, surgical patients, and obstetric patients. There are many terms used to describe this life-threatening problem, including **massive transfusion coagulopathy** or **trauma-induced coagulopathy (TIC)**. The complex coagulopathy that occurs in these situations further compromises the efficacy of subsequent hemostatic treatments. Tissue injury due to trauma, surgical interventions, following delivery in obstetric patients, or associated with extracorporeal circulation during cardiopulmonary bypass or extracorporeal membrane oxygenation may also contribute to the coagulopathic state.

Hemostasis is a physiologic response to vascular injury and disruption of the vascular endothelium and has been described in earlier chapters. Following surgery or trauma where there is extensive tissue injury, in addition to massive loss of blood, the endothelial integrity is compromised; the coagulopathy that follows tissue injury and blood loss produces a complex alteration in the vasculature often described as an **endothelialopathy**. Loss of the critical aspects of vascular regulation can also manifest as disseminated intravascular coagulation, a perturbation of the balance between anticoagulant and procoagulant effects.

TIC also has some unique characteristics due to two major causes that include hypovolemic shock that results from blood loss and extensive tissue disruption. Additional important considerations are the traumatic injury and extent of tissue injury, other underlying factors based on the potential for multiorgan dysfunction, and the resuscitation used, including fluids versus blood components, use of pharmacologic approaches such as antifibrinolytics and/or factor concentrates. Thus, the extensive blood loss and potential for multiorgan tissue injury and/or dysfunction distinguishes TIC from other coagulopathic states.

In addition, the management of hemostasis following traumatic injury and life-threatening hemorrhage has significantly changed over the years from initial resuscitation with crystalloid/colloids and red blood cells (RBCs) to routine administration of plasma/fresh frozen plasma (FFP) and platelets in addition to red cells, and currently goal-directed management based on point-of-care testing including viscoelastic measurements. Experiences learned from the battlefield and civilian studies have been critical for developing multiple therapeutic approaches that have been combined in a rational massive transfusion protocol. Retrospective studies have reported improved survival with the initial use of plasma and platelets as part of these protocols. This chapter reviews the physiology of massive transfusion and modern therapeutic approaches.

Pathophysiology of Hemostatic Abnormalities Associated With Trauma

Hemorrhage is a major cause of mortality following traumatic injury and responsible for approximately 50% of deaths within 24 hours of injury and approximately 80% of intraoperative trauma deaths.¹ The evolution of fluid resuscitation initially included crystalloid, followed by RBC transfusions, and the addition of FFP/plasma, platelets, and cryoprecipitate either empirically or as guided by additional laboratory testing. Therapy in the past was based on treating coagulopathy after the initial resuscitation and stabilization of the patient. More recent observations in trauma victims and on the battlefield found that early administration of plasma resulted in earlier improvement, whereas several studies reported that use of large crystalloid volumes was associated with increased bleeding and lower survival.^{1–3}

Trauma and Endothelial Dysfunction

The effects of hemorrhagic shock on endothelial function have been described, and the term **endotheliopathy of trauma** has been proposed to describe the systemic endothelial injury and dysfunction that contributes to

coagulopathy, inflammation, vascular permeability, tissue edema, and multiorgan system dysfunction.^{1,2} The endothelial dysfunction is secondary to vascular injury and other factors that result from shock, ischemic injury, and the release of inflammatory mediators. Plasma repletion is thought to have a restorative function on endothelial tight junctions to better modulate vascular integrity compared to crystalloid studying in vitro models. Plasma contains multiple serine protease inhibitors that may have antiinflammatory effects. The endothelium becomes permeable with hemorrhagic shock, and extravascular fluid is mobilized intravascularly. Plasma contains proteins for osmotic maintenance, but there are also multiple serine protease inhibitors that include antithrombin (also called **antithrombin III**), C1 esterase inhibitor, tissue factor pathway inhibitor, plasminogen activator inhibitor-1 (PAI-1), α_2 -antiplasmin, and other inhibitors that may be critical for antiinflammatory responses. Crystalloids lack these factors and are thought to increase interstitial edema, increase lung injury, and promote multiorgan system dysfunction.^{1,2}

Inflammatory activation following tissue injury contributes to the endothelial dysfunction, as does the critical role of fibrinolysis. With tissue injury, the fibrinolytic system is activated converting plasminogen to plasmin, a critical enzyme that cleaves fibrin. Plasmin and its generation are inhibited by plasminogen activator inhibitor-1, by thrombin-activatable fibrinolysis inhibitor, and by α_2 -antiplasmin. Thus, fibrinolysis is regulated by multiple circulating serine protease inhibitors under physiologic conditions that can be depleted with massive hemorrhage. As a result of this pathologic activation, antifibrinolytic therapy is a critical component of a multimodal approach, the success of which has been reported in multiple patient populations undergoing surgery. In addition to contributing to a bleeding diathesis, plasmin generation causes a multitude of other effects, including cell signalling, proinflammatory responses, and activation of the complement cascade.⁴

Massive Transfusion

Massive transfusion is defined as greater than 10 units of RBCs within 24 hours after initiating treatment and occurs in approximately 10% of military trauma and approximately 5% of civilian trauma patients.¹⁻³ Patients who acutely bleed and receive greater than 10 units of RBCs within 6 hours of a trauma have a higher mortality. However, the massive transfusion itself is likely a marker for more severe injury rather than a direct effect of the transfusions. The development of massive transfusion strategies and use of specific protocols improve survival and have been an important evolution in the management of trauma patients, wartime injuries, and even massive hospital bleeds that occur following postpartum hemorrhage or massive surgical bleeding. Other important clinical indicators of massive transfusion as reported by Cap et al³ include systolic blood pressure <110 mm Hg, heart rate >105 beats per minute, hematocrit <32%, pH <7.25, injury pattern (above-the-knee traumatic amputation especially if pelvic injury is present, multiamputation, clinically obvious penetrating injury to chest or abdomen), >2 regions positive on focused assessment with sonography for trauma scan, lactate concentration on admission >2.5, admission international normalized ratio \geq 1.2 to 1.4, near-infrared spectroscopy-derived tissue oxygen saturation <75% (in practice, rarely available), and base deficit >6 mEq/L.

Therapeutic Approaches for Massive Transfusion and Coagulopathy

Transfusion services, blood bankers, clinicians, and hospitals have developed and implemented protocols to rapidly provide blood products for patients suffering acute and massive hemorrhage. Observational studies and retrospective analyses of military and civilian trauma initially reported improved outcomes with the administration of whole blood or whole blood equivalents with massive transfusion that include transfusion ratios of 1:1:1 for RBCs, plasma, and platelets.^{1,2}

Additional recommendations suggest adding cryoprecipitate to the component mix to create a 1:1:1:1 ratio of products in order to adequately supply fibrinogen and other clotting factors (factors VIII and XIII and von Willebrand factor) and again in an effort to reconstitute fresh whole blood. However, point-of-care monitoring, and other goal-directed therapy can follow with fibrinogen levels and facilitate additional potential therapeutic approaches.³

Adverse Effects of Transfusions

All transfusions have risk, and certain concerns regarding plasma are important. Major life-threatening risks of plasma administration include transfusion-related acute lung injury, transfusion-associated circulatory overload, hemolytic transfusion reactions, and anaphylaxis (these phenomena have been discussed in an earlier chapter, [Chapter 28, Blood Products and Blood Components](#)). Deciphering the causes of adverse outcomes following transfusions can be difficult because more critically injured patients who have worse outcomes will also require more transfusions, and the reason underlying the need for transfusion will invariably cloud any interpretation of the clinical outcomes.

Hemostatic Changes Associated With Massive Transfusion Coagulopathy

Hemostatic abnormalities following massive transfusions and/or trauma can develop as a result of multiple factors not necessarily directly related to blood administration. Along with coagulopathy, hypothermia and acidosis complete the triad that results in higher mortality in the management of acute trauma. These factors may play a role in the localized depletion or decreased function of hemostatic factors through blood loss, tissue injury, and/or consumption of factors. Volume resuscitation with crystalloids, colloids, and RBCs or the use of cell salvage systems following blood loss can lead to dilutional coagulopathy. The hemostatic balance between anticoagulant and procoagulant activity may be lost due to tissue injury following trauma (including head trauma), tissue hypoxia/acidosis, burns/sepsis, or other physical events especially in an intraoperative setting from suction and reinfusion of debris.

Hypothermia can be a critical factor that precipitates or worsens coagulopathy, as enzymatic cascades are impaired; this impairment may appear beginning at even small drops in core body temperatures, even as high as 35°C. Platelet function may also be impaired with hypothermia, and platelet dysfunction can also occur due to fibrinolysis that increase fibrinogen degradation products, including D-dimer levels.⁴ Other important considerations include anemia-related factors, that is, decreased RBC adenosine diphosphate and decreased platelet diffusivity; and the effects of acidemia, which may include hypocalcemia with massive transfusions.

Perioperative Hemostatic Changes

Trauma and surgical patients have varied degrees of vascular injury, coagulopathy, and exsanguination.⁵ Blood loss up to 30% of total blood volume is generally well tolerated with the fluid resuscitation alone. Coagulation factors are progressively diluted to 30% of normal after a loss of one blood volume and down to 15% after a loss of two blood volumes.⁶ With severe hemodilution, thrombin generation, a critical step in clot formation is impaired by a reduction in procoagulant levels. Thrombin generation is also impaired by thrombocytopenia. Additionally, fibrinogen and factor XIII, critical substrates for clot formation, also decrease without appropriate factor replacement during volume resuscitation. Although clot may form, low levels of fibrinogen and/or factor XIII will result in reduced clot strength, a finding that is often monitored with viscoelastic blood monitoring using thromboelastography (TEG) or rotational thromboelastometry (ROTEM). Low levels of clotting proteins affect the ability of fibrin to polymerize.⁶

Massive Transfusion Coagulopathy

Because standard laboratory tests often take too long to obtain, and with severe hemorrhage, several blood volumes may be replaced by the time the results are available, laboratory testing plays an uncertain role in decision making in many settings where massive transfusion is necessary. Thus, transfusion protocols have been developed where fixed doses of FFP and platelets are administered after a specific number of RBC units have been given, often in a 1:1:1 ratio.^{1-4,6-8} Whether these fixed ratios prevent the development of coagulopathy or improve bleeding is not well established in cardiac surgery, but in trauma patients and in noncardiac surgical battlefield conditions, multiple previous reports suggested that fixed ratios improve survival.^{7,8}

With life-threatening bleeding, as seen in trauma patients, transfusion of fixed ratios of RBCs, FFP, and platelets should be administered.⁶ Transfusion with fixed plasma/FFP:platelet:RBC ratios reports a survival

benefit. As a result, the Army Surgeon General established a clinical policy of 1:1:1 (plasma/FFP:platelets:RBCs) for combat casualties expected to receive massive transfusion. One large study of civilian massive transfusion patients demonstrated improved survival with increased use of platelets.⁸ The current U.S. military resuscitation practice is to use a balanced approach, using 1:1:1 as the primary resuscitation fluid for the most seriously injured casualties. Current studies are underway to determine what the optimal ratios should be in a variety of clinical settings.

Role of Red Blood Cells and Anemia

Anemia may also contribute to bleeding as reported in nonsurgical patients due to multiple mechanisms that include nitric oxide scavenging, margination of platelets, and contributions to the hemostatic processes, although the ideal hematocrit to minimize this risk is not clear. RBC transfusions are administered for multiple reasons, and they are increasingly recognized for their critical role in hemostasis. RBCs can release adenosine diphosphate, an important activator of platelets. Platelets also contribute a surface for clot initiation by facilitating thrombin generation.⁶ Studies suggest that the factor XIII activation and fibrin cross-linking may play an important role in mediating RBC retention within clots.

Causes of Bleeding in the Setting of Massive Transfusion Coagulopathy

Risk factors for developing massive transfusion coagulopathy are often related to the surgical or traumatic injury that causes the hemorrhage. Patients should be evaluated for use of additional medications that can affect coagulation, including antiplatelet agents (clopidogrel, prasugrel, ticagrelor), anticoagulation agents (dabigatran, rivaroxaban, apixaban, warfarin), or parenteral agents such as low-molecular-weight heparin.⁹ Monitoring these agents has been reviewed in other chapters. Many of the standard coagulation tests used for evaluating hemorrhage cannot adequately determine the effects of antiplatelet agents (eg, aspirin, clopidogrel, prasugrel, or ticagrelor) as the complex platelet function tests used clinically are usually ineffective with significant bleeding (see [Chapter 30, Anticoagulants](#)).

Hypothermia, Acidosis, and Coagulopathy

Hypothermia has multiple effects because coagulation is an enzymatic process. As patient temperature decreases, the enzymatic processes that function maximally at normal body temperature are impaired. Hypothermia can produce multiple hemostatic defects that include reversible platelet dysfunction and increased fibrinolysis.¹ In addition, prothrombin time (PT) and activated partial thromboplastin time are prolonged at temperatures of 34°C or less when compared with measurements at 37°C.¹ When blood is sampled from a hypothermic patient, the test is actually conducted at 37°C, so the influence of hypothermia on coagulopathy and bleeding may not be readily appreciated by clinicians. Overall, hypothermia is an important contributing factor to the bleeding defect in coagulopathy in trauma patients and is part of the lethal triad defined as hypothermia, acidosis, and coagulopathy. Hypothermia and acidosis can also prevent thrombin generation, a critical component of clot formation. Hypothermia is thought to inhibit the initiation phase, whereas acidosis severely inhibits the propagation phase of thrombin generation.¹⁰ Maintenance of normothermia is important as part of a multimodal therapeutic plan for minimizing blood loss with significant hemorrhage in trauma, surgery, or coagulopathy of any cause. In a perioperative setting, blood warmers and other warming devices should be used to prevent and treat hypothermia.

Dilutional Coagulopathy

Before the development of massive transfusion protocols, dilutional coagulopathy was a common cause of bleeding in the actively hemorrhaging patient. Bleeding and coagulopathy associated with massive transfusions in 21 acutely traumatized soldiers that occurred after transfusion of 20 to 25 units of stored whole blood was described.¹¹ In this report, dilutional thrombocytopenia was a primary cause of the bleeding and was thought to be due to decreased platelet levels in stored blood. Transfusion of approximately 15 to 20 units caused significant dilution of blood volumes, and critical decreases in platelet count to approximately 20,000 to 30,000/ μ L, far below the recommended platelet target goals in actively bleeding patients.¹¹

Fibrinolysis

Fibrinolysis is a critical component of preventing excessive clot formation and balances for hemostasis, but excessive fibrinolysis as occurs commonly in trauma patients can cause bleeding. Fibrinolysis is initiated by mechanisms that include stimulating tissue plasminogen activator release in response to vascular endothelial damage, stress responses, and other mechanisms.⁴ Plasmin degrades fibrinogen and von Willebrand factor, cleaves receptors from platelets (glycoprotein Ib), and creates degradation products that bind glycoprotein IIb/IIIa receptors, thus interfering with platelet function. Contact activation associated with tissue injury and hemostatic activation also activates kallikrein that initiates plasmin generation but also is involved in other proinflammatory steps including neutrophil chemotaxis and chemokinesis.⁴ Contact activation leads to the cleaving of glycoprotein Ib receptors from platelets, and generation of FDP resulted in the creation of multimers that bind with glycoprotein IIb/IIIa receptors to prevent platelet-fibrinogen cross-linking, alterations in fibrinolysis adversely affect platelet function.⁴

Hypofibrinogenemia

Fibrinogen is a critical component in clot formation and an acute-phase reactant protein. Fibrinogen circulates in the highest concentration of all of the coagulation factors, and normal values for plasma levels are approximately 200 to 400 mg/dL but increase in pregnancy and as a nonspecific anabolic postoperative response following tissue injury.^{12,13} In the late stages of pregnancy, the normal physiologic response is hypercoagulability to reduce the risk of bleeding complications during birth. Although benign dilutional thrombocytopenia often develops, with a platelet count of 80,000 to 150,000/ μ L, fibrinogen levels increase to approximately 400 to 600 mg/dL. During delivery, a systemic hemostatic state develops with consumption of platelets and coagulation factors (including fibrinogen) to allow clotting to occur; hemostasis then normalizes within 4 to 6 weeks postpartum.¹³

If fibrinogen levels fall to approximately 80 to 100 mg/dL, standard clot-based coagulation tests including PT and partial thromboplastin time, can be affected. These changes may not be corrected by transfusion of FFP/plasma; however, cryoprecipitate is used or fibrinogen concentrates in countries that do not have cryoprecipitate (see [Chapters 27-30](#)). Current transfusion algorithms and guidelines are focused on targeting normal fibrinogen levels (\sim 200 mg/dL = 2 g/L) in the bleeding patient with either cryoprecipitate or fibrinogen concentrates depending upon the availability.^{12,13}

Monitoring Hemostasis During Massive Transfusion

PT and activated partial thromboplastin time are often used for monitoring coagulopathy during massive transfusion. The PT is considered proportional to coagulation factor loss and/or hemodilution, but other factors may also be responsible. These standard coagulation tests have limitations for evaluating bleeding because of the multiple coagulation defects that occur. Standard plasma-based coagulation tests also do not provide information about platelet function or interactions with coagulation factors and can be prolonged even with normal clotting factor levels due to protein C deficiency. As a result, other coagulation tests are being used more and more for managing massive transfusions.

Whole blood viscoelastic measurements continue to expand for management of trauma, perioperative bleeding, and massive transfusion coagulopathy and include either TEG (Haemonetics Corp, Braintree, MA) or Rotational thromboelastometry (ROTEM) (Instrumentation Laboratory, Bedford, MA). Some of the advantages of using these systems include the ability to rapidly have information for the diagnosis and management of coagulopathy and also provide methods for algorithm- and goal-directed management. ROTEM provides information about clot formation and fibrin polymerization, and its use is recommended in multiple guidelines to assess and treat TIC. The clot strength, as determined by maximal amplitude on TEG and maximal clot firmness on ROTEM, is influenced not only by fibrinogen levels but also by platelet contributions to the clot. In addition, using the ROTEM fibrinogen-FIBTEM assay, systemic fibrinogen levels can be rapidly determined. The role of these advanced tests during massive transfusion continues to evolve as therapeutic strategies for transfusion and treatment algorithms are developed. In European countries where

cryoprecipitate may not be available, these assays are used as therapeutic guides for both fibrinogen concentrate and prothrombin complex concentrate administration.⁶

Treatment of Coagulopathy During Massive Transfusion

A flow chart and example for the activation and institution of a massive transfusion protocol are shown in **Figures 31.1** and **31.2**. Specific considerations for the management have been discussed and are also included in the following perspectives regarding individual component therapy.

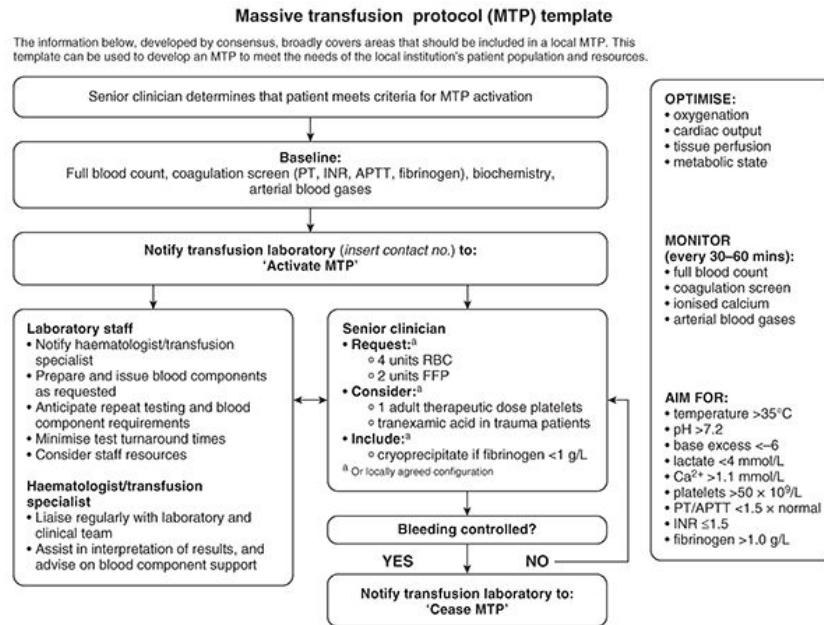


FIGURE 31.1 Massive transfusion protocol template. Abbreviations: APTT, activated partial thromboplastin time; FFP, fresh frozen plasma; INR, international normalized ratio; PT, prothrombin time; RBC, red blood cell. Reprinted with permission from *Patient blood management guidelines: Module 1 – Critical bleeding/Massive transfusion*. Copyright © National Blood Authority, 2011. ISBN 978-0-9775298-5-8.

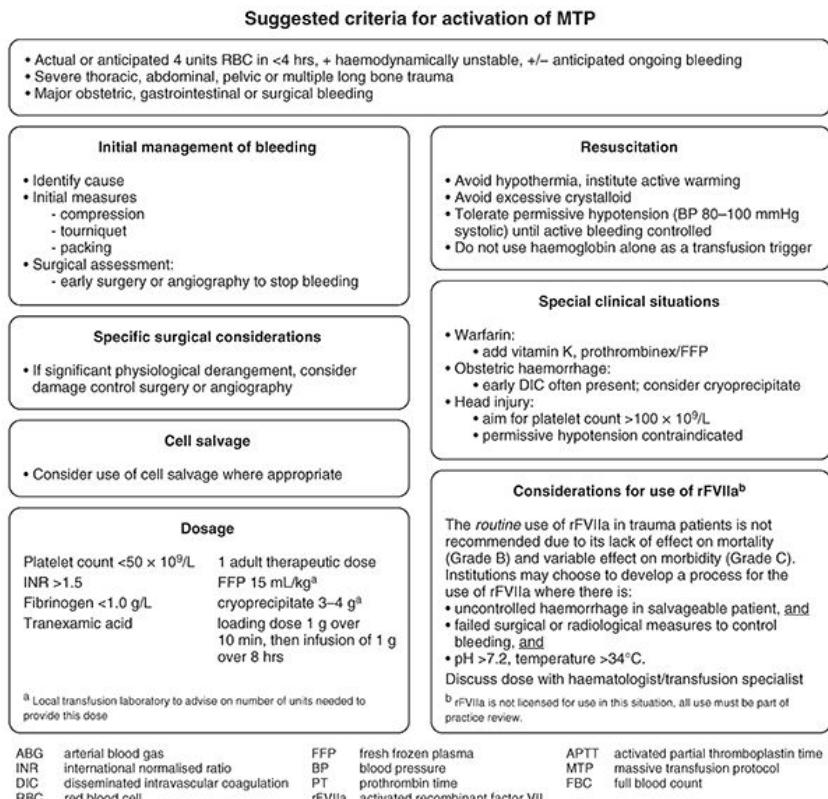


FIGURE 31.2 Suggested criteria for activation of massive transfusion protocol (MTP) template. Note as listed in b for activated recombinant factor VII (rFVIIa) use, current algorithms have increasingly used this procoagulant and rather consider prothrombin complex concentrates based on coagulation testing (see [Chapter 29, Procoagulants](#)). Reprinted with permission from *Patient blood management guidelines: Module 1 – Critical bleeding/Massive transfusion*. Copyright © National Blood Authority, 2011. ISBN 978-0-9775298-5-8

Plasma/Fresh Frozen Plasma

Overall, developing massive transfusion protocols has been an important therapeutic tool for effectively managing life-threatening hemorrhage after trauma, as previously reviewed.¹⁴ Plasma/FFP contains multiple factors for hemostasis and has increasingly been considered an important component. Based on current data and recommendations previously described, current plasma/FFP transfusion:RBC ratios of 1:1 following trauma is recommended and used in most centers for massive transfusion coagulopathy.³

The optimal ratio of plasma/FFP:RBCs was evaluated prospectively in a randomized clinical trial of 680 severely injured patients in North America.¹⁵ Blood product ratios of 1:1:1 (338 patients) versus 1:1:2 (342 patients) during active resuscitation in addition to all local standard-of-care interventions. Primary outcomes were 24-hour and 30-day all-cause mortality. There were no significant differences in mortality at 24 hours (12.7% in 1:1:1 group vs 17.0% in 1:1:2 group) or at 30 days (22.4% vs 26.1%, respectively).

Exsanguination, which was the predominant cause of death within the first 24 hours, was decreased in the 1:1:1 group (9.2% vs 14.6% in 1:1:2 group), and more patients in the 1:1:1 group achieved hemostasis than in the 1:1:2 group (86% vs 78%). Despite the 1:1:1 group receiving more plasma (median of 7 U vs 5 U, $P < .001$) and platelets (12 U vs 6 U, $P < .001$) and similar amounts of RBCs (9 U) over the first 24 hours, no differences between the two groups were found for complications acute lung injury, organ failure, or other prespecified adverse events.¹⁵

There are major differences in the management of severe hemorrhage between the United States and Europe. Based on currently published European guidelines, clinicians are now using factor concentrates

based on ROTEM guidance, with prothrombin complex concentrates, fibrinogen, and factor XIII. Fibrinogen and other factor concentrates have been used for many years in Europe, as cryoprecipitate is not available in all countries. However, therapy is multimodal and requires hemodynamic and hemostatic support as well as efforts to address the underlying bleeding source. An example of a massive transfusion protocol is shown in [Figure 31.1](#).⁶

Platelet Administration

Following traumatic injury or significant postoperative bleeding, the critical platelet count for transfusion is often based on consensus therapy rather than true objective data. Although a count of 50,000 or more is recommended, the threshold for the administration of platelets, especially in cases of dilutional coagulopathy, remains unclear as do the ideal ratio of platelets to other blood components. Most protocols attempt to develop a strategy that mimics whole blood replacement with RBC:plasma/FFP:platelets at a 1:1:1 ratio with massive bleeding.

However, assessing platelet function in the bleeding patient is not possible; therefore, empiric platelet administration is often undertaken. If patients have received antiplatelet agents recently, then even the existing platelets and platelet counts may not be helpful. Therefore, if patients have received antiplatelet agents or are bleeding after separation from cardiopulmonary bypass, then platelet dysfunction should be suspected, and platelet concentrates considered. However, there are significant potential adverse events associated with platelet administration.

Antifibrinolytic Agents

Because of the critical role of fibrinolysis with severe bleeding and trauma, the antifibrinolytic agent tranexamic acid is increasingly used as a therapeutic strategy. Inhibiting fibrinolysis during acute bleeding has many beneficial effects, including preserving initial clot formation at a bleeding site that may otherwise be broken down, similar to the clot destruction seen in hemophilia.⁴

The Clinical Randomisation of an Antifibrinolytic in Significant Hemorrhage 2 study focused on tranexamic acid as a therapeutic agent in traumatic injury in a prospective randomized placebo-controlled trial of 1-g loading followed by 1 g over 8 hours in 20,211 trauma patients.¹⁶ Overall mortality was reduced from 14.5% to 16.0% (relative risk, 0.91; $P = .0035$), as were deaths due to bleeding (4.9% vs 5.7%; relative risk, 0.85; $P = .0077$). Tranexamic acid is also approved in the United States for excessive menstrual bleeding at a dose of 1.3 g 3 times a day (~4 g total dose), without significant reported safety issues. Despite the efficacy and safety of tranexamic acid, clinicians often substitute epsilon-aminocaproic acid, another lysine analog, although this agent has not been studied as well as tranexamic acid and is not available in some European countries.

Procoagulants

Multiple other agents have been used or studied in trauma, and massive transfusion coagulopathy, including prothrombin complex concentrates. The off-label use of many of these agents to increase clot formation following major surgery and/or traumatic injury previously was an empiric approach for treating life-threatening bleeding and often used as a “last-ditch effort” in patients with ongoing bleeding and at risk for death or other adverse events. However, based on recommendations to use viscoelastic monitoring in massive transfusion coagulopathy and following traumatic coagulopathy, many algorithms suggest the use of prothrombin complex concentrates when clot time on EXTEM is abnormal, or there’s a prolonged PT/international normalized ratio value with life-threatening hemorrhage.^{4,12}

Goal-Directed Management

In the future, we may treat our severely injured trauma patients based on their phenotype. We suggest that specific treatment strategies for TIC, like tranexamic acid administration, should be individualized based on shock end points such as base deficit, as shock and/or tissue injury are potential factors that influence either a thrombotic or a bleeding phenotype. Clinicians should consider early goal-directed therapy based on diagnostic testing including viscoelastic assays. They should also be aware of potential that may alter trauma

phenotypes over time, including antiplatelet or anticoagulant therapy, gender, injury pattern, and hemostatic resuscitation.

Postpartum Hemorrhage

Postpartum hemorrhage is an important cause of life-threatening hemorrhage and continues to be a major cause of maternal mortality.¹⁷ A recent published report from an international expert panel in obstetrics, gynecology, anesthesiology, hematology, and transfusion medicine performed a comprehensive literature review to identify patients at high risk for adverse outcomes.¹⁷ They defined severe persistent postpartum hemorrhage as “active bleeding greater than 1,000 mL within the 24 hours following birth that continues despite the use of initial measures, including first-line uterotonic agents and uterine massage.” As in all life-threatening bleeding, a treatment algorithm that includes a massive transfusion protocol is important. The group suggested coagulation testing should be performed to guide therapy. If initial therapy fails to stop bleeding and uterine atony persists, second- and third-line interventions, including mechanical or surgical maneuvers, that is, intrauterine balloon tamponade or hemostatic brace sutures with hysterectomy, are the final surgical option for uncontrollable bleeding.¹⁷ Pharmacologic options include hemostatic agents, including tranexamic acid along with a massive transfusion protocol for blood product administration are also critical to minimize blood loss and optimize clinical outcomes in management of women with severe, persistent postpartum hemorrhage.¹⁷

Multimodal Resuscitation: Damage Control Resuscitation

Managing life-threatening and uncontrolled bleeding is a clinical problem that can occur following traumatic injury, during major surgical procedures, and following delivery. From information learned from combat and battlefield casualties, a multimodal and multispecialty approach has evolved that includes perspectives from surgeons, anesthesiologists, emergency medicine physicians, and transfusion medicine specialists for the optimal resuscitative approach to hemorrhagic shock.¹⁻³ Clinicians and investigators from multiple specialties have coined the term **damage control resuscitation**, a multimodal strategy.³ This concept is a strategy for resuscitating patients to rapidly restore homeostasis. As described by Cap et al,³ the multimodal approaches focus on transfusions with whole blood or component therapy to reconstitute whole blood administration, limited crystalloid to avoid dilutional coagulopathy, hypotensive resuscitation until bleeding control is achieved, empiric use of tranexamic acid, prevention of acidosis and hypothermia, and rapid definitive surgical control of bleeding.

Summary

Coagulopathy associated with massive transfusion is a complex, multifactorial clinical problem. When evaluating the causes of coagulopathy in this setting, preexisting pharmacotherapy, including prior use of anticoagulants, must be considered. The role of hypothermia, dilutional coagulopathy, platelet dysfunction, and fibrinolysis should also be considered. Evaluating fibrinogen levels represents a critical aspect of all transfusion algorithms, especially for patients with massive transfusion and life-threatening hemorrhage. Transfusion algorithms are a critical and relatively new aspect of perioperative management; they attempt to provide adequate factor and hemostatic replacement, although the ideal ratio of various blood components and factor concentrates are still being determined. Significant changes in management have become important in resuscitation strategies, and crystalloids are no longer a primary means of resuscitation; the primary strategy now is replacing acute blood loss with plasma and platelet-containing products instead of early and large amounts of crystalloids and RBCs. Templates for a massive transfusion protocol and activation of a massive transfusion protocol are included in [Figures 31.1](#) and [31.2](#). Several excellent reviews are available for additional reading on this subject.^{1,3,5,18}

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PART VI Gastrointestinal System and Metabolism

Gastrointestinal Physiology

Michael J. Murray

Liver

In humans, the liver is the largest organ, and because of the multitude of metabolic functions that occur within its cells, it is also the most exothermic organ, thereby contributing significantly to the maintenance of core temperature. The liver lies in the right upper quadrant (although a small portion extends across the midline, just below the xiphoid process, into the left upper quadrant) just below the diaphragm where it is protected by the ribcage.¹ Hepatocytes comprise 60% of the total number of cells in the liver but, because of their size in comparison to other hepatic cells,² represent approximately 80% of the cytoplasmic mass within the liver. These cells perform diverse and complex functions ([Table 32.1](#)).

TABLE 32.1

Functions of hepatocytes

Absorb nutrients from portal venous blood
Store and release carbohydrates, proteins, and lipids
Excrete bile salts
Synthesize glucose, plasma proteins, coagulation factors, lipoproteins, cholesterol, and fatty acids
Metabolize and detoxify drugs and toxins
Bilirubin uptake, conjugation, and secretion

Hepatocytes have been derived from stem cells for several years, but more recently, those derived from extended pluripotent stem cells are reported to have considerable differentiation potential.³ They are being grown in culture systems to produce organoids that are being studied in bioartificial livers and liver fabrication.⁴

Anatomy

The right and left lobes of the liver are separated by the falciform ligament on the cephalad (diaphragmatic) surface and by the venous and round ligaments on the caudal (visceral) surface. The gallbladder, inferior vena cava, and hilum delineate a quadrate and a caudate lobe in the right lobe of the liver. These anatomic landmarks were not particularly helpful when surgeons began operating on the liver, so a model based on the vascular and biliary systems within the liver was developed.⁵ Newer technologies are being used to gain additional insights into the architecture of the liver,^{2,6} but the concepts developed by Couinaud and Nogueira⁵ remain a widely accepted model described in textbooks. Couinaud divided the liver into “surgical” segments that have independent biliary drainage and vascular supply.⁷ This functional approach to the liver, using these segments as guides, facilitated liver resections with minimal blood loss.

The hepatic artery perfuses the liver with oxygenated blood, whereas the portal vein perfuses the liver with blood flowing from the small intestine that has high concentrations of nutrients. The blood flows through liver sinusoids, which are terminal blood vessels lined with endothelial and Kupffer cells and surrounded by hepatocytes ([Figure 32.1](#)).^{1,2}

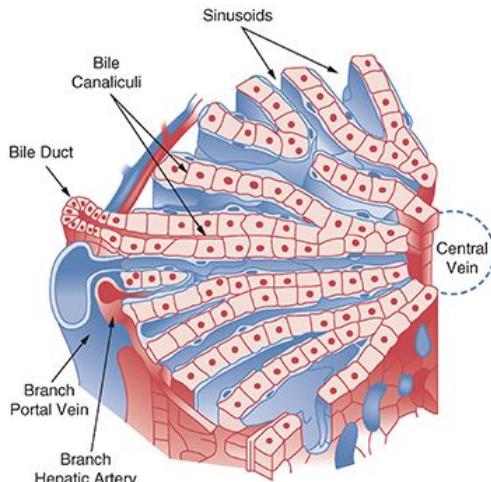


FIGURE 32.1 Schematic depiction of a hepatic lobule with a central vein and plates of hepatocytes extending radially. Blood from peripherally located branches of the hepatic artery and vein perfuses the sinusoids. Bile ducts drain the bile canaliculi that pass between the hepatocytes.

There is usually only one layer of hepatocytes between sinusoids, so the total area of contact with plasma is great. Blood flowing through the sinusoids exits these structures into branches of hepatic veins, the smallest of which are called central veins or terminal hepatic veins. Central veins join to form hepatic veins, which coalesce into two to three large hepatic veins that drain directly into the inferior vena cava.

Each hepatocyte is also located adjacent to bile canaliculi, which coalesce to form the common hepatic duct. This duct and the cystic duct from the gallbladder join to form the common bile duct, which enters the duodenum at a site surrounded by the sphincter of Oddi (Figure 32.2). The main pancreatic duct unites with the common bile duct just before it enters the duodenum.

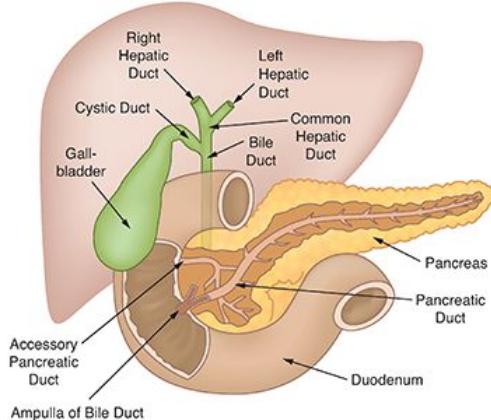


FIGURE 32.2 Connections of the ducts of the gallbladder, liver, and pancreas.

Kupffer cells mentioned earlier are macrophages that are derived from circulating monocytes. They phagocytize 99% or more of bacteria in the portal venous blood. This is crucial because the portal venous blood drains the gastrointestinal tract and usually contains bacteria.

Hepatic stellate cells are located between the endothelium of the sinusoids and the hepatocytes. These cells are normally quiescent, but in response to liver injury secrete collagen, and if the injury is prolonged, the result is fibrosis and ultimately cirrhosis.

Sinusoids are well adapted for the function they serve. They are fenestrated vascular structures without a basement membrane permitting easy diffusion of macromolecules transported via the portal vein from the gastrointestinal tract including plasma lipoproteins, into extravascular spaces of the liver that connect with terminal lymphatics. The extreme permeability of the endothelium results in the formation of large quantities

of lymph, which contains protein concentrations that are only slightly less than the protein concentration of plasma. Approximately one-third to one-half of all lymph are formed in the liver.

Hepatic Blood Flow

The liver receives a dual afferent blood supply from the hepatic artery and the portal vein ([Figure 32.3](#)). Total hepatic blood flow is approximately 1,972 mL per minute or approximately 30% to 40% of the cardiac output.⁸ Of this amount, the portal vein provides ~80% of the total flow but only 50% to 55% of the hepatic oxygen supply because this blood is partially deoxygenated in the organs and tissues (gastrointestinal tract, spleen, pancreas) drained by the portal vein.⁸ The hepatic artery provides only 20% of total hepatic blood flow but provides 45% to 50% of the hepatic oxygen requirements. Hepatic artery blood flow maintains the viability of connective tissues and walls of bile ducts. For this reason, loss of hepatic artery blood flow can be fatal because of ensuing necrosis of vital liver structures. An increase in hepatic oxygen requirements is met by an increase in oxygen extraction rather than a further increase in the already high hepatic blood flow.

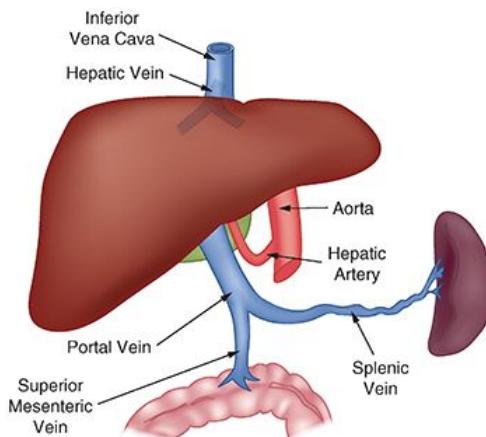


FIGURE 32.3 Schematic depiction of the dual afferent blood supply to the liver provided by the portal vein and hepatic artery.

Control of Hepatic Blood Flow

The control of the afferent blood supply to the liver, coming from both the hepatic artery and portal vein, is complicated. The portal vein has no valves but otherwise is similar to other veins in that the venous flow is through a low-resistance, low-pressure venous system in the liver, terminating in the hepatic sinusoids. Blood flow through the portal vein is a function of the constriction or relaxation of splanchnic arterioles and the resistance within the intrahepatic venous system, which determines portal venous pressure (normally 7-10 mm Hg) (see the “[Portal Venous Pressure](#)” section).

The hepatic artery on the other hand is a high-resistance, high-pressure system in which flow is very much determined by cardiac output and the autonomic nervous system.⁹ Activation of the sympathetic nervous system not only constricts hepatic arterioles but also decreases the permeability of hepatic sinusoids, the net effect of which is a decrease in total hepatic blood flow. Release of norepinephrine by efferent sympathetic nerve terminals induces contraction of hepatic arterioles and hepatic sinusoids. Efferent parasympathetic nerve terminal release of acetylcholine and vasoactive intestinal peptide stimulates relaxation of hepatic arterioles and sinusoids. Thus, the sinusoids have a critical role in reducing hepatic blood flow during hemorrhage and ultimately contribute to the maintenance of circulating blood volume. Similarly, sympathetic innervation of hepatic venules is principally responsible for resistance and compliance of hepatic venules.⁹ Constriction of hepatic venules shifts blood from the liver into the systemic circulation, accounting for the reservoir function of the liver (see the “[Reservoir Function](#)” section).

Fibrotic constriction characteristic of hepatic cirrhosis (most often due to chronic alcohol abuse and hepatitis C) can increase resistance to portal vein blood flow, as evidenced by portal venous pressures of 20 to

30 mm Hg (portal hypertension). The resulting increased resistance to portal vein blood flow may result in development of shunts (varices) to allow blood flow to bypass the hepatic sinusoids. Hepatic artery blood flow is influenced by arteriolar tone that reflects local and intrinsic mechanisms (autoregulation). For example, a decrease in portal vein blood flow is accompanied by an increase in hepatic artery blood flow by as much as 100%. Presumably, a vasodilating substance such as adenosine accumulates in the liver when portal vein blood flow decreases, leading to subsequent hepatic arteriolar vasodilation and washout of the vasodilating material.

Congestive hepatopathy develops when right-sided cardiac failure leads to hepatic venous outflow obstruction secondary to increased right atrial pressure.¹⁰

Cirrhotic cardiomyopathy is a clinical entity in which cirrhosis impairs ventricular function in response to stress in the absence of other potential causes of cardiac disease. “Stress” may include reaction to drugs, intravascular volume shifts and exercise, and surgical interventions, for example, transjugular intrahepatic portosystemic shunts and liver transplant.¹¹

Isoflurane, desflurane, and sevoflurane when administered in equal potent doses decrease hepatic blood flow to a similar degree.^{12–14} In contrast to these inhalation anesthetics, halothane decreased hepatic blood flow to a greater extent but preserved autoregulation of hepatic blood flow, although only to a limited extent and only when used in doses that did not decrease systemic blood pressure >20%.¹⁵ Surgical stimulation may further decrease hepatic blood flow, independent of the anesthetic drug administered. The greatest decreases in hepatic blood flow occur during intra-abdominal operations, presumably due to mechanical interference of blood flow produced by retraction in the operative area as well as the release of vasoconstricting substances such as catecholamines.

Reservoir Function

The liver normally contains approximately 500 mL of blood or approximately 10% of the total blood volume. An increase in central venous pressure causes back pressure, and the liver, being a distensible organ, may accommodate as much as 1 L of extra blood. As such, the liver acts as a storage site when blood volume is excessive, as in congestive heart failure, and is capable of supplying extra blood when hypovolemia occurs. Indeed, the hepatic sinusoids and large hepatic veins, when constricted by stimulation from the sympathetic nervous system, discharge up to 350 mL of blood into the circulation. Therefore, the liver is the single most important source of additional blood during strenuous exercise or acute hemorrhage.

Bile Secretion

Hepatocytes continually form bile (500 mL daily) and then secrete it into bile canaliculi, which empty into progressively larger ducts, ultimately reaching the common bile duct (see [Figure 32.2](#)).¹⁶ Between meals, the tone of the sphincter of Oddi, which guards the entrance of the common bile duct into the duodenum, is high.¹⁷ As a result, bile flow is diverted into the gallbladder, which has a capacity of 35 to 50 mL. The most potent stimulus for emptying the gallbladder is the presence of fat in the duodenum, which evokes the release of the hormone cholecystokinin by the duodenal mucosa. This hormone enters the circulation and passes to the gallbladder, where it causes selective contraction of the gallbladder smooth muscle. As a result, bile is forced from the gallbladder into the duodenum. When adequate amounts of fat are present, the gallbladder empties in approximately 1 hour. The principal components of bile are bile salts, bilirubin, and cholesterol.

Bile Salts

Bile salts combine with lipids in the duodenum to form water-soluble complexes (micelles) that facilitate gastrointestinal absorption of fats (triglycerides) and fat-soluble vitamins. Once absorbed, bile salts return to the liver via the portal vein, where they enter hepatocytes (enterohepatic circulation).¹⁸ In the absence of bile secretion, steatorrhea and a deficiency of vitamin K develop in a few days. Vitamin K is necessary for activation of several of the clotting factors that contain glutamic acid residues.

Bilirubin

After approximately 120 days, the cell membranes of erythrocytes rupture, and the released hemoglobin is converted to bilirubin in reticuloendothelial cells. Bilirubin is then released into the circulation and transported in combination with albumin to the liver. Bilirubin is a hydrophobic tetrapyrrole that is conjugated in the liver to glucuronic acid, and the resulting compound is then excreted in urine and bile. The importance of this process is significant for 200 to 300 mg of bilirubin is produced daily in adults from the degradation of hemoglobin and cellular cytochromes ([Figure 32.4](#)).¹⁹ Unlike conjugated bilirubin, unconjugated bilirubin may be neurotoxic and may even cause a rapidly fatal encephalopathy. In the gastrointestinal tract, bilirubin is converted by bacterial action mainly into urobilinogen.

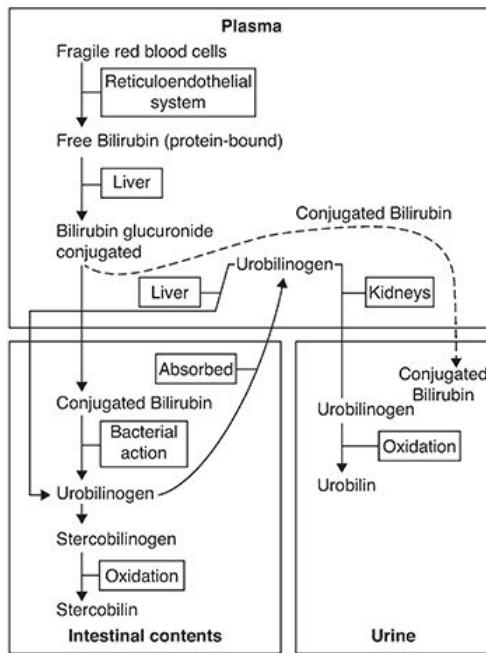


FIGURE 32.4 Schematic depiction of bilirubin formation and excretion. Reprinted from Guyton AC, Hall JE. Textbook of Medical Physiology. 10th ed. Philadelphia, PA: W.B. Saunders; 2000. Copyright © 2000 Elsevier. With permission.

Jaundice

Jaundice is the yellowish tint of body tissues that accompanies accumulation of bilirubin in extracellular fluid. Skin color usually begins to change when the plasma concentration of bilirubin increases to approximately 3 times normal. The most common types of jaundice are hemolytic jaundice, due to increased destruction of erythrocytes, and obstructive jaundice, due to obstruction of bile ducts.²⁰

Cholesterol

Almost every cell in the body can synthesize all the cholesterol they need for it is an important component of cell walls (synthesized in tissues from acetate in a reaction catalyzed by β -hydroxy β -methylglutaryl coenzyme A), but only the liver can eliminate cholesterol. It is transported from the periphery to the liver as high-density lipoproteins and once there can be excreted in the bile in its unesterified form or in association with bile acids.²¹ Cholesterol in the bile may precipitate as gallstones if there is excess absorption of water in the gallbladder or the diet contains too much cholesterol. Gallstones occur in 10% to 20% of individuals; 85% are cholesterol stones.

Metabolic Functions

Metabolism of carbohydrates, lipids, and proteins depends on normal hepatic function (see [Chapter 33](#)). Furthermore, the liver is an important storage site for vitamins and iron. Degradation of certain hormones

(catecholamines and corticosteroids), as well as drugs, is an important function of the liver. Hepatocytes are the principal site for synthesis of all the coagulation factors, with the exception of von Willebrand factor and factor VIIIC. Because the half-life of clotting factors produced in the liver is short, coagulation is particularly sensitive to acute hepatocellular damage.

Carbohydrates

Regulation of blood glucose concentration is another important metabolic function of the liver. When hyperglycemia is present, glycogen is deposited in the liver, and when hypoglycemia occurs, glycogenolysis provides glucose. Amino acids can be converted to glucose in hepatocytes by gluconeogenesis when the blood glucose concentration is decreased.

Lipids

The liver is responsible for β -oxidation of fatty acids and formation of acetoacetic acid. Triglycerides are formed from the esterification of glycerol with three molecules of fatty acid. Pancreatic lipases and esterases are important in facilitating the absorption of dietary fats. After absorption, fat may be stored as triglycerides (reserve energy) or metabolized to energy. Lipoproteins, cholesterol, and phospholipids, such as lecithin, are formed in the liver. Synthesis of fats from carbohydrates and proteins also occurs in the liver.²¹

Proteins

The most important hepatic functions in protein metabolism are oxidative deamination of amino acids, formation of urea for removal of ammonia, formation of plasma proteins and coagulation factors, and interconversions (transfer of one amino group to another amino acid) among different amino acids. Albumin formed in the liver is critically important for maintaining plasma oncotic pressure as well as providing an essential transport role. The half-life for albumin is about 21 days; therefore, plasma albumin concentrations are unlikely to be significantly altered in acute hepatic failure. Deamination of amino acids is required before these substances can be used for energy or converted into carbohydrates or fats. Decreases in portal vein blood flow, as may occur with the surgical creation of a portacaval shunt to treat esophageal varices, can result in fatal hepatic coma because of accumulation of ammonia.

Gastrointestinal Tract

The primary function of the gastrointestinal tract is to provide the body with a continual supply of water, electrolytes, and nutrients. To achieve this goal, the contents of the gastrointestinal tract must move through the entire system at an appropriate rate for digestive and absorptive functions to occur. Each part of the gastrointestinal tract is adapted for specific functions such as (1) passage of food in the esophagus, (2) storage of food in the stomach or fecal matter in the colon, (3) digestion of food in the stomach and small intestine, and (4) absorption of the digestive end products and fluids in the small intestine and proximal parts of the colon. Overall, approximately 9 L of fluid and secretions enter the gastrointestinal tract daily, and all but approximately 100 mL is absorbed by the small intestine and colon ([Figure 32.5](#)). The pH of gastrointestinal secretions varies widely ([Table 32.2](#)).

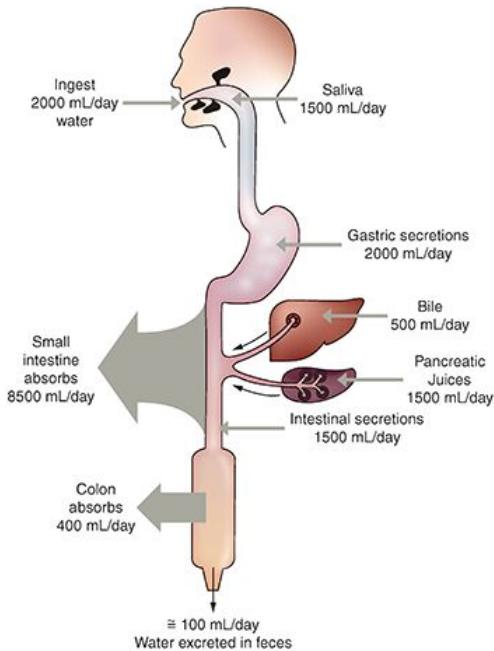


FIGURE 32.5 Overall fluid balance in the human gastrointestinal tract. Approximately 2 L of water are ingested each day, and approximately 7 L of various secretions enter the gastrointestinal tract. Of this 9 L, about 8.5 L are absorbed from the small intestine. Approximately 0.5 L passes to the colon, which normally absorbs 80% to 90% of the water presented to it. *From Berne RM, Levy MN, Koeppen BM, et al. Physiology. 5th ed. St Louis, MO: Mosby; 2004. Reprinted with permission from Bruce M. Koeppen, MD.*

TABLE 32.2	
pH and gastrointestinal secretions	
Secretions	pH
Saliva	6-7
Gastric fluid	1.0-3.5
Bile	7-8
Pancreatic fluid	8.0-8.3
Small intestine	6.5-7.5
Colon	7.5-8.0

Anatomy

The smooth muscle of the gastrointestinal tract is a syncytium such that electrical signals originating in one smooth muscle fiber are easily propagated from fiber to fiber. Mechanical activity of the gastrointestinal tract is enhanced by stretch and parasympathetic nervous system stimulation, whereas sympathetic nervous system stimulation decreases mechanical activity to almost zero.

Tonic contraction of gastrointestinal smooth muscle at the pylorus, ileocecal valve, and anal sphincter helps regulate the rate at which materials move through the gastrointestinal tract. In these parts of the gastrointestinal tract, rhythmic movements (peristalsis) occur 3 to 12 times per minute to facilitate mixing and movement of food.²²

Blood Flow

Most of the blood flow to the gastrointestinal tract comes from the celiac and superior mesenteric and inferior mesenteric arteries to supply oxygen needed to produce energy for intestinal digestion and absorption of

digested materials. Blood flow parallels digestive activity of the gastrointestinal tract. Approximately 80% of portal vein blood flow originates from the stomach and gastrointestinal tract, with the remainder coming from the spleen and pancreas.

Parasympathetic efferent fibers traveling through the vagus nerve effect normal gastrointestinal function, dilating arterioles, promoting smooth muscle contraction, and stimulating glandular secretions for digestion. Activation of sympathetic fibers promotes just the opposite, constricting arterioles and inhibiting motility, digestion, and absorption.²³ The decrease in blood flow, however, is transient because local metabolic vasodilator mechanisms elicited by the relatively ischemic mucosa return blood flow toward normal. The importance of this transient sympathetic nervous system–induced vasoconstriction is that it permits shunting of blood from the gastrointestinal tract for brief periods during exercise or when increased blood flow is needed by skeletal muscles or the heart.

Portal Venous Pressure

The liver offers modest resistance to blood flow from the portal venous system. As a result, the pressure in the portal vein averages 7 to 10 mm Hg, which is considerably higher than the almost zero pressure in the inferior vena cava. Cirrhosis of the liver is characterized by increased resistance to portal vein blood flow due to replacement of hepatic cells with fibrous tissue that constricts the hepatic sinusoids. The gradual increase in resistance to portal vein blood flow produced by cirrhosis of the liver causes large collateral vessels to develop between the portal veins and the systemic veins. The most important of these collaterals are from the splenic veins to the esophageal veins. These collaterals may become so large that they protrude into the lumen of the esophagus, producing esophageal varicosities. The esophageal mucosa overlying these varicosities may become eroded, leading to life-threatening hemorrhage.²⁴

Another consequence of cirrhosis is the development of ascites, which is due to inability to compensate for the increased splanchnic arterial vasodilation secondary to portal hypertension. To maintain arterial blood volume, vasoconstrictor and antinatriuretic biochemicals are released, which increase systemic sodium and fluid retention. As portal hypertension worsens, in the face of increased intravascular volume, there is an increase in the capillary pressure on the intestinal surface, with the transudation of protein-poor fluid into the abdominal cavity. Ascitic fluid can also translocate across the diaphragm into the right chest creating a hepatic hydrothorax. Patient with ascites can develop spontaneous bacterial peritonitis, which associated with high mortality.²⁵

Splenic Circulation

The splenic capsule in humans, in contrast to that in many lower animals, is nonmuscular, which limits the ability of the spleen to release large amounts of stored blood in response to sympathetic nervous system stimulation. However, a small amount (150-200 mL) of blood stored in the splenic venous sinuses and can be released by sympathetic nervous system–induced vasoconstriction of the splenic vessels. Release of this amount of blood into the systemic circulation is sufficient to increase the hematocrit 1% to 2%. There is evidence that this neural modulation of the spleen contributes to the development of “idiopathic” or “essential” hypertension.²⁶

The spleen functions to remove erythrocytes from the circulation. This occurs when erythrocytes reenter the venous sinuses from the splenic pulp by passing through pores that may be smaller than the erythrocyte. Fragile cells do not withstand this trauma, and the released hemoglobin that results from their rupture is ingested by the reticuloendothelial cells of the spleen. These same reticuloendothelial cells also function, much like lymph nodes, to remove bacteria and parasites from the circulation. Indeed, asplenic patients are more prone to developing bacterial infections.

During fetal life, the splenic pulp produces erythrocytes in the same manner as does the bone marrow in the adult. As the fetus reaches maturity, however, this function of the spleen is lost. The spleen is the largest lymphoid organ with a multitude of immunologic functions in addition to its role in erythrocyte clearance. The anatomic structure of the spleen facilitates clearance of abnormal cells and pathogens and promotes interaction of lymphocytes with antigen-bearing cells. These antigen-bearing cells in essence regulate B and T cell response to the antigens they transport to the spleen.²⁷

Innervation

The gastrointestinal tract receives innervation from both divisions of the autonomic nervous system as well as from an intrinsic nervous system consisting of the myenteric plexus, or Auerbach plexus, and the submucous plexus, or Meissner plexus. In the absence of sympathetic nervous system or parasympathetic nervous system stimulation, the motor and secretory activities of the gastrointestinal tract continue, reflecting the function of the intrinsic nervous system. Signals from the autonomic nervous system can and do influence the activity of the intrinsic nervous system. For example, impulses from the parasympathetic nervous system increase intrinsic activity, whereas signals from the sympathetic nervous system decrease intrinsic activity. A large number of neuromodulatory substances act in the gastrointestinal tract.²³

The cranial component of parasympathetic nervous system innervation to the gastrointestinal tract (esophagus, stomach, pancreas, small intestine, colon to the level of the transverse colon) is by way of the vagus nerves. The distal portion of the colon is richly supplied by the sacral parasympathetics via the pelvic nerves from the hypogastric plexus. Fibers of the sympathetic nervous system destined for the gastrointestinal tract pass through ganglia such as the celiac ganglia.

Motility

The two types of gastrointestinal motility are mixing contractions and propulsive movements characterized as **peristalsis**. The usual stimulus for peristalsis is distension. Peristalsis occurs only weakly in portions of the gastrointestinal tract that have congenital absence of the myenteric plexus. Peristalsis is also decreased by increased parasympathetic nervous system activity and anticholinergic drugs.

Ileus

Trauma to the intestine or irritation of the peritoneum as follows abdominal operations causes adynamic (paralytic) ileus. Peristalsis returns to the small intestine in 6 to 8 hours, but colonic activity may take 2 to 3 days. Adynamic ileus can be relieved by a tube placed into the small intestine and aspiration of fluid and gas until the time when peristalsis returns.

Salivary Glands

The principal salivary glands (parotid and submaxillary) produce 0.5 to 1.0 mL per minute of saliva (pH 6-7), largely in response to parasympathetic nervous system stimulation. Saliva washes away pathogenic bacteria in the oral cavity as well as food particles that provide nutrition for bacteria. In the absence of saliva, oral tissues are likely to become ulcerated and infected. The bicarbonate ion concentration in saliva is 2 to 4 times that in plasma, and the high potassium content of saliva can result in hypokalemia and skeletal muscle weakness if excess salivation persists.

Esophagus

The esophagus serves as a conduit for passage of food from the pharynx to the stomach. The swallowing or deglutition center located in the medulla and lower pons inhibits the medullary ventilatory center, halting breathing at any point to allow swallowing to proceed. The upper and lower ends of the esophagus function as sphincters to prevent entry of air and acidic gastric contents, respectively, into the esophagus. The sphincters are known as the **upper esophageal (pharyngoesophageal) sphincter** and **lower esophageal (gastroesophageal) sphincter**.

Lower Esophageal Sphincter

The lower esophageal sphincter regulates the flow of food between the esophagus and the stomach. The sphincter mechanism at the lower end of the esophagus consists of the intrinsic smooth muscle of the distal esophagus and the skeletal muscle of the crural diaphragm. Under normal circumstances, the lower esophageal sphincter is approximately 4 cm long. The crural diaphragm, which forms the esophageal hiatus, encircles the proximal 2 cm of the sphincter. The intraluminal pressure of the esophagogastric junction is a measure of the strength of the antireflux barrier and is typically quantified with reference to the intragastric pressure (normal <7 mm Hg). Both the lower esophageal sphincter and the crural diaphragm contribute to the

intragastric pressure. Muscle tone in the lower esophageal sphincter is the result of neurogenic and myogenic mechanisms. A substantial part of the neurogenic tone in humans is due to cholinergic innervation via the vagus nerves. The presynaptic neurotransmitter is acetylcholine, and the postsynaptic neurotransmitter is nitric oxide.

The normal lower esophageal sphincter pressure is 10 to 30 mm Hg at end exhalation. Transient relaxation of the lower esophageal sphincter is a neural reflex mediated through the brainstem. Gastric barrier pressure is calculated as lower esophageal sphincter pressure minus intragastric pressure. This barrier pressure is considered the major mechanism in preventing reflux of gastric contents into the esophagus. Gastric distension, meals high in fat, and pharyngeal stimulation are possible mechanisms by which the afferent stimulus that initiates transient relaxation of the lower esophageal sphincter may originate. Cricoid pressure decreases lower esophageal sphincter pressure, presumably reflecting stimulation of mechanoreceptors in the pharynx created by the external pressure on the cricoid cartilage ([Figure 32.6](#)). General anesthesia decreases lower esophageal sphincter pressure 7 to 14 mm Hg, depending on the degree of skeletal muscle relaxation. Normally, upper esophageal sphincter pressure prevents regurgitation into the pharynx in the awake state. The administration of anesthetic drugs may decrease upper esophageal sphincter pressure even before the loss of consciousness.

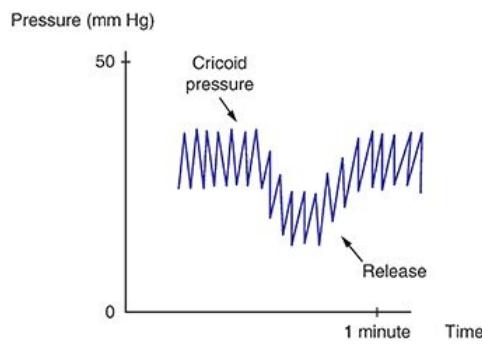


FIGURE 32.6 Application of cricoid pressure causes the lower esophageal sphincter pressure to decrease.
Reprinted by permission from Springer: Chassard D, Tournadre JP, Berrada KR, et al. Cricoid pressure decreases lower oesophageal sphincter tone in anaesthetized pigs. Can J Anaesth. 1996;43(4):414-417. Copyright © 1996 Springer Nature.

Despite decreases in lower esophageal sphincter pressure associated with anesthesia, the incidence of gastroesophageal reflux is rare in patients undergoing elective operations.[28](#)

Gastroesophageal Reflux Disease

Transient relaxation of the lower esophageal sphincter, rather than decreased lower esophageal sphincter pressure, is the major mechanism of gastroesophageal reflux disease (GERD). Transient relaxation of the lower esophageal sphincter is associated with simultaneous inhibition of the sphincter and crural diaphragm. Some patients with gastroesophageal reflux have a weak lower esophageal sphincter, some have a weak crural diaphragm, and some have both. In GERD, the reflux of gastric fluid into the esophagus or oropharynx causes symptoms (esophagitis characterized as “heartburn”) and/or tissue damage, leading over time to the development of Barrett esophagus. It is estimated that approximately 20% of adults in the United States experience symptoms of GERD at least weekly, and many patients with severe GERD have a hiatal hernia.

Opioids decrease the frequency of transient relaxation of the lower esophageal sphincter in normal patients through an unknown mechanism.[29](#) Antisecretory drugs such as histamine receptor antagonists or proton pump inhibitors may be useful in treating gastroesophageal reflux. Therapy with a prokinetic drug such as metoclopramide may be effective. Patients with severe gastroesophageal reflux may benefit from surgical fundoplication of the esophagus via a laparoscopic technique.

Hiatal Hernia

The majority of patients with moderate to severe gastroesophageal reflux have a hiatal hernia in which a portion of the stomach herniates into the chest. Hiatal hernia may promote gastroesophageal reflux by trapping gastric acid in the hernia sac, which may then flow backward into the esophagus when the lower esophageal sphincter relaxes during swallowing. Hiatal hernia can also cause gastroesophageal reflux when contraction of the crural diaphragm during inspiration and other physical maneuvers lead to a compartmentalization of the stomach between the lower esophageal sphincter and the diaphragm. The presence of acid in the esophagus causes esophagitis, which decreases the lower esophageal sphincter pressure and impairs esophageal contractility.

Achalasia

Achalasia is the best characterized of all esophageal motility disorders reflecting degeneration of neurons in the wall of the esophagus, especially the nitric oxide-producing inhibitory neurons that affect the relaxation of esophageal smooth muscle necessary for opening the lower esophageal sphincter. The loss of inhibitory innervation in the lower esophageal sphincter causes basal sphincter pressure to increase and interferes with sphincter relaxation. In the body of the esophagus, the loss of intramural neurons manifests as aperistalsis. Dysphagia for both solid foods and liquids is the primary symptom of achalasia. A substantial number of patients complaining of heartburn may have achalasia, which may therefore be confused with GERD.

Achalasia can be confirmed with radiographic (barium swallow shows dilatation of the esophagus with a beaklike narrowing of esophagogastric junction), manometric, and endoscopic evaluation (often performed utilizing drugs to produce sedation). The diagnosis may be suggested by a routine radiograph of the chest that shows widening of the mediastinum from the dilated esophagus and the absence of the normal gastric air bubble because lower esophageal sphincter contraction prevents swallowed air from entering the stomach.

Nitrates and calcium channel blockers relax the smooth muscle of the lower esophageal sphincter and may produce limited success in treating patients with achalasia. Pneumatic dilation therapy for achalasia (a large deflated balloon is passed through the mouth to the lower esophageal sphincter and then rapidly inflated) may be helpful. Esophageal perforation is a risk of this treatment. Surgical myotomy of the lower esophageal sphincter performed laparoscopically often results in excellent relief but may be followed by GERD. For this reason, the myotomy may be combined with an antireflux procedure (fundoplication). Endoscopic injection of botulinum toxin into the area of the lower esophageal sphincter blocks the excitatory (acetylcholine-releasing) neurons that contribute to lower esophageal sphincter tone. Unfortunately, the effect is usually short lived (less than 6 months).³⁰ A patient with achalasia presenting for surgery unrelated to the underlying esophageal motility disorder represents a potential risk for pulmonary aspiration during the perioperative period.

Stomach

The stomach is a specialized organ of the digestive tract that stores and processes food for digestion ([Figure 32.7](#)). The ability to secrete hydrogen ions in the form of hydrochloric acid is a hallmark of gastric function. The secretory unit of gastric mucosa is the oxyntic glandular mucosa. The stomach is richly innervated by the parasympathetic fibers from the vagus nerves and sympathetic fibers from the celiac plexus.

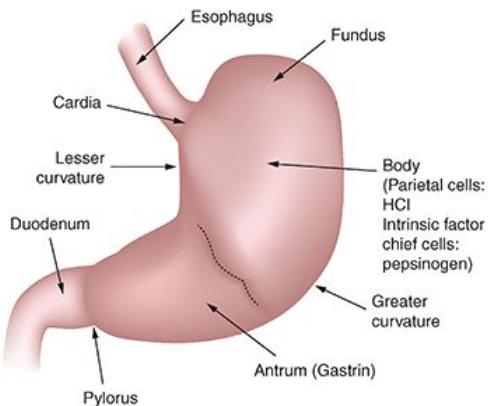


FIGURE 32.7 Anatomy of the stomach indicating the site of production of secretions. Mucus is secreted in all parts of the stomach.

Gastric Secretions

Total daily gastric secretion is approximately 2 L with a pH of 1.0 to 3.5. The stomach secretes only a few milliliters of gastric fluid each hour during the periods between digestion. Strong emotional stimulation, such as occurs preoperatively, can increase secretion of highly acidic gastric fluid to >50 mL per hour. The major secretions are hydrochloric acid, pepsinogen, intrinsic factor, and mucus. Mucous secretion protects the gastric mucosa from mechanical and chemical destruction. Substances that disrupt the mucosal barrier and cause gastric irritation include ethanol and drugs that inhibit prostaglandin synthesis (aspirin, nonsteroidal antiinflammatory drugs).

Parietal Cells

Parietal cells secrete a hydrogen ion-containing solution with a pH of approximately 0.8. At this pH, the hydrogen ion concentration is approximately 3 million times that present in the arterial blood. Hydrochloric acid kills bacteria, aids protein digestion, provides the necessary pH for pepsin to start protein digestion, and stimulates the flow of bile and pancreatic juice.

Secretion of hydrochloric acid depends on stimulation of receptors in the membrane of parietal cells by histamine, acetylcholine (vagal stimulation), and gastrin. All of these receptors increase the transport of hydrogen ions into the gastric lumen by the hydrogen-potassium-adenosine triphosphatase enzyme system ([Figure 32.8](#)). Activation of one receptor type potentiates the response of the other receptors to stimulation. Blockade of receptors with specific antagonist drugs produces effective decreases in acid transport responses by removing the potentiating effect of stimulation of these receptors on the responses to other stimuli. Blockade of muscarinic receptors is produced by atropine or the more specific anticholinergic pirenzepine. Gastrin receptors can be inhibited by proglumide. Alternatively, the hydrogen-potassium-adenosine triphosphatase enzyme system can be inhibited by omeprazole. Pharmacologic manipulation of gastric fluid pH has special implications in the management of patients considered to be at risk for pulmonary aspiration during the perioperative period.

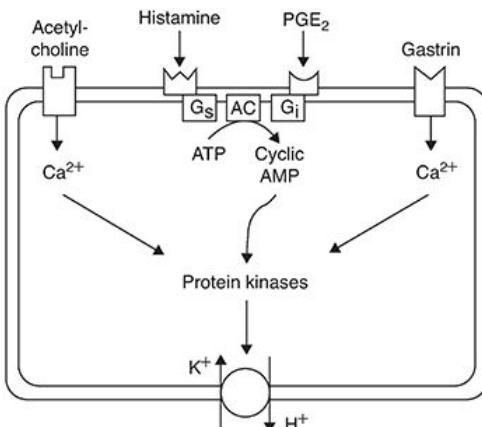


FIGURE 32.8 Gastric hydrogen ion secretion by parietal cells is increased by acetylcholine and gastrin acting on responsive receptors to increase intracellular calcium. Histamine activates receptors to activate stimulatory guanine proteins (G_s) to increase adenylate cyclase (AC) activity, whereas prostaglandins (PGE_2) activate inhibitory guanine proteins (G_i) to decrease AC activity. Cyclic adenosine monophosphate (cyclic AMP) and calcium act via protein kinases to increase transport of hydrogen ions into the gastric lumen.
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Intrinsic factor, which is essential for absorption of vitamin B_{12} from the ileum, is secreted by parietal cells. For this reason, destruction of parietal cells, as is associated with chronic gastritis, produces achlorhydria and often pernicious anemia.

Chief Cells

Pepsinogens secreted by chief cells undergo cleavage to pepsins in the presence of hydrochloric acid. Pepsins are proteolytic enzymes important for the digestion of proteins.

G Cells

Gastrin is secreted by gastric antral cells (G cells) into the circulation, which carries this hormone to responsive receptors in parietal cells to stimulate gastric hydrogen ion secretion. Gastrin also increases the tone of the lower esophageal sphincter and relaxes the pylorus.

Gastric Fluid Volume and Rate of Gastric Emptying

Neural and humoral mechanisms greatly influence gastric fluid volume and gastric-emptying time. As discussed previously, parasympathetic nervous system stimulation enhances gastric fluid secretion and motility, whereas sympathetic nervous system stimulation has an opposite effect. The elimination of nonnutritive liquids is an exponential process (volume of liquid emptied per unit of time is directly proportional to the volume present in the stomach), whereas the emptying of solids is a linear process (Figure 32.9). In this regard, emptying of liquids from the stomach begins within 1 minute of ingestion, whereas emptying of solids typically begins after a lag time of 15 to 137 minutes (median 49 min). Gastric emptying in healthy, term, nonobese parturients is not delayed compared to nonpregnant women.³¹ It is generally thought that the delay in gastric emptying of solids is caused by the time necessary for antral contractions to break solids down into small enough particles to exit through the pylorus. Clinical manifestations of delayed gastric emptying include anorexia, persistent fullness after meals, abdominal pain, and nausea and vomiting.

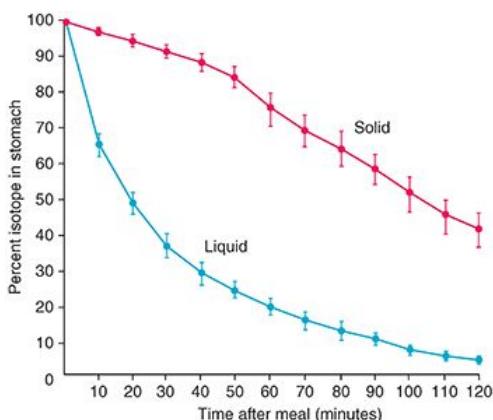


FIGURE 32.9 Gastric emptying of liquids is exponential, whereas emptying of solids is a linear process.

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Several factors affect the rate of gastric emptying.³² The primary determinant of the emptying of liquids from the stomach is volume. In addition to volume, another factor that influences the rate of gastric emptying is the composition of the liquids. Emptying of neutral, iso-osmolar, and calorically inert solutions is rapid (250 of 500 mL of normal saline is emptied in 12 min). A small amount of water (up to 150 mL) to facilitate administration of oral medications shortly before the induction of anesthesia does not produce sustained increases in gastric fluid volume and could even contribute to gastric emptying. Solutions that are hypertonic or contain acid, fat, or certain amino acids all retard gastric emptying. High lipid and/or caloric content slows the emptying of solids from the stomach.^{18,23}

Hyperglycemia, impaired neural control, and neuromuscular inflammatory processes are all thought to play a role in the development of diabetic gastroparesis.³³ As many as 50% of patients with moderately controlled diabetes mellitus type I and II exhibit delayed gastric emptying, which can be demonstrated with carbon 13 breath tests, scintigraphy or a wireless motility capsule. Delayed gastric emptying of solids is the most consistent abnormality in diabetics with gastroparesis, but this parallels normal physiology whereby liquids pass through the pylorus exponentially depending on the volume and composition of the liquid, whereas solids pass through much more slowly in a biphasic manner. There is an initial lag period in which solids are digested to particles ≤ 2 mm in size and then a more rapid linear phase mimicking that of liquids.³³ As diabetes progresses, it is possible that gastric retention of liquids will also occur.

Patients with GERD and documented slowing of gastric emptying of solids have been shown to have normal gastric emptying rates for liquids. Most patients with slowed gastric emptying of solids in association with GERD do not demonstrate symptoms such as nausea and vomiting, which are usually associated with gastric stasis. The existence of delayed gastric emptying in gastric ulcer disease is controversial. Some data suggest a slowing of gastric emptying of solids but not liquids in the presence of gastric ulcers. Although obesity and pregnancy are often assumed to slow gastric emptying, there are also data that fail to confirm this slowing, whereas other data suggest accelerated gastric emptying in obese individuals. Contraction of the gastric fundus is responsible for facilitating the emptying of liquids, whereas antral contractions control the emptying of solids, after they have been digested into smaller particles.

Gastrointestinal transit time has been shown to vary during the menstrual cycle, with prolongation occurring during the luteal phase when progesterone levels are increased. Acute viral gastroenteritis has been associated with delayed gastric emptying.

Certain drugs, including opioids, β -adrenergic agonists, and tricyclic antidepressants, may slow gastric emptying. Aluminum hydroxide antacid may slow gastric emptying. Alcohol, at least in concentrations present in wine, does not significantly affect gastric emptying of liquids or solids. Higher concentrations of alcohol, such as present in whiskey, do cause slowing of gastric emptying. The mechanism of this slowing is not clear but may be due to hyperosmolarity, changes in gastric acid secretion, or damage to gastric mucosa.

Total parenteral nutrition may cause gastric stasis. Elemental diets, probably due to their high concentration of amino acids and hyperosmolarity, take longer to empty from the stomach than does blenderized food of comparable caloric composition. Cigarette smoking has been shown to delay emptying of solids, although it may accelerate emptying of liquids. Gastric prokinetic drugs such as metoclopramide may speed the emptying of solids and liquids. New therapeutic regimens demonstrating potential to treat delayed gastric emptying include ghrelin receptor agonists and selective 5-hydroxytryptamine receptor agonists.³³

Gastric Emptying Prior to Elective Surgery

Clear liquids can be administered to adult patients scheduled for elective operations until 2 hours before induction of anesthesia without increasing gastric fluid volume. It takes 3 to 4 hours for the stomach to empty following a light breakfast (one slice of white bread with butter and jam, 150 mL of coffee without milk or sugar, 150 mL of pulp-free orange juice). These data are consistent with the most recent recommendations from the most recent American Society of Anesthesiologists that a 6-hour fast should be enforced after a light breakfast.³⁴ However, there are a number of Enhanced Recovery after Surgery protocols that are somewhat more lenient. Because of the heterogeneity of these protocols, it is not possible to recommend that oral nutrition support improves the condition of patients undergoing colorectal surgery, the group of patients for whom Enhanced Recovery after Surgery was initially developed,³⁵ and therefore, the issue of preoperative fasting remains somewhat controversial.³⁶

Opioid-Induced Slowing of Gastric Emptying

Opioids receptors are found throughout the gastrointestinal system with particularly high concentrations in the gastric antrum and proximal duodenum. Central and peripheral μ -opioid receptors can regulate gastric emptying, and opioid-induced delay in gastric emptying can be reversed with naloxone, which acts simultaneously at both central and peripheral sites. The demonstration that methylnaltrexone, a selective peripheral-acting opioid antagonist, attenuates morphine-induced changes in the rate of gastric emptying indicates that peripheral opioid receptors modulate this response in humans (see [Chapter 7](#)).³⁷

Measurement of the Rate of Gastric Emptying

As mentioned earlier, the rate of gastric emptying can be evaluated by carbon 13 breath tests, scintigraphy, or by use of a wireless motility capsule.³³ Potentially of more interest to anesthesiologists is the use of ultrasonography both to measure gastric volume preoperatively³⁸ and, from a research perspective, to measure the rate of gastric emptying.³⁹ This technology is increasingly being used throughout the United States and at least for certain procedures is considered a standard of care.

Vomiting

Vomiting is coordinated by the vomiting center in the medulla. This center receives input from multiple sites including the chemoreceptor trigger zone in the floor of the fourth ventricle, from the vestibular apparatus, from cortical centers, and from the gastrointestinal tract. The blood–brain barrier is poorly developed around the chemoreceptor trigger zone, and emetic substances present in the circulation are readily accessible to this site. Serotonin acting at 5-hydroxytryptamine receptors ($5-HT_3$) is an important emetic signal via neural pathways from the gastrointestinal tract ending at the chemoreceptor trigger zone. Likewise, dopamine and acetylcholine may provide emetic signals to the chemoreceptor trigger zone. Pharmacologic antagonism of these emetic signals results in antiemetic effects. The role of specific opioid receptors in emetic responses is unresolved. Following stimulation of the vomiting center (directly or indirectly via neural pathways), vomiting is mediated by efferent pathways including the vagus and phrenic nerves, and innervation of the abdominal musculature. The initial manifestation of vomiting often involves nausea in which gastric peristalsis is reduced or absent and the tone of the upper small intestine is increased and gastric reflux occurs. The next steps involve the closure of the glottis with simultaneous contraction of the diaphragm, which creates significantly negative intrathoracic pressure. The pylorus and abdominal muscles contract greatly increasing intragastric pressure. The final step is coordinated relaxation of the upper stomach and lower and

upper esophageal sphincters, which leads to explosive expulsion of gastric contents. Risk factors for postoperative nausea and vomiting include female sex, young age (children), history of motion sickness, abstinence from tobacco, and obesity (perhaps reflecting emetic anesthetic drugs stored in adipose tissue).

Small Intestine

The small intestine consists of the duodenum (from the pylorus to the ligament of Treitz), the jejunum, and the ileum (ending at the ileocecal valve). There is no distinct anatomic boundary between the jejunum and ileum, but the first 40% of small intestine after the ligament of Treitz is often considered the jejunum. The small intestine is presented with approximately 9 L of fluid daily (2 L from the diet and the rest representing gastrointestinal secretions), but only 1 to 2 L of chyme enters the colon. The small intestine is the site of most of the digestion and absorption of proteins, fats, and carbohydrates ([Table 32.3](#)).

TABLE 32.3

Site of absorption

	Duodenum	Jejunum	Ileum	Colon
Glucose	++	+++	++	0
Amino acids	++	+++	++	0
Fatty acids	+++	++	+	0
Bile salts	0	+	+++	0
Water-soluble vitamins	+++	++	0	0
Vitamin B ₁₂	0	+	+++	0
Sodium	+++	++	+++	+++
Potassium	0	0	+	++
Hydrogen	0	+	++	++
Chloride	+++	++	+	0
Calcium	+++	++	+	?

Chyme moves through the 5 meters of small intestine at an average rate of 1 cm per minute. As a result, it takes 3 to 5 hours for chyme to pass from the pylorus to the ileocecal valve. On reaching the ileocecal valve, chyme may remain in place for several hours until the person eats another meal. An inflamed appendix can increase the tone of the ileocecal valve to the extent that emptying of the ileum ceases. Conversely, gastrin causes relaxation of the ileocecal valve. When more than 50% of the small intestine is resected, the absorption of nutrients and vitamins is so compromised that development of malnutrition is likely.

Secretions of the Small Intestine

Mucous glands (Brunner glands) present in the first few centimeters of the duodenum secrete mucus to protect the duodenal wall from damage by acidic gastric fluid. Stimulation of the sympathetic nervous system inhibits the protective mucus-producing function of these glands, which may be one of the factors that cause this area of the gastrointestinal tract to be the most frequent site of peptic ulcer disease.

The crypts of Lieberkühn contain epithelial cells that produce up to 2 L daily of secretions that lack digestive enzymes and mimic extracellular fluid, having a pH of 6.5 to 7.5. This fluid provides a watery vehicle for absorption of substances from chyme as it passes through the small intestine. The most important mechanism for regulation of small intestine secretions is local neural reflexes, especially those initiated by distension produced by the presence of chyme.

The epithelial cells in the crypts of Lieberkühn continually undergo mitosis, with an average life cycle of approximately 5 days. This rapid growth of new cells allows prompt repair of any excoriation that occurs in the mucosa. This rapid turnover of cells also explains the vulnerability of the gastrointestinal epithelium to chemotherapeutic drugs (see [Chapter 42](#)).

The epithelial cells in the mucosa of the small intestine contain digestive enzymes that most likely are responsible for digestion of food substances because they are absorbed across the gastrointestinal epithelium. These enzymes include peptidases for splitting peptides into amino acids, enzymes for splitting disaccharides into monosaccharides, and intestinal lipases.

Absorption From the Small Intestine

Mucosal folds (valvulae conniventes), microvilli (brush border), and epithelial cells provide an absorptive area of approximately 250 m^2 in the small intestine for nearly all the nutrients and electrolytes as well as approximately 95% of all the water. Daily absorption of sodium is 25 to 35 g, emphasizing the rapidity with which total body sodium depletion can occur if excessive intestinal secretions are lost as occurs with extreme diarrhea. Active transport of sodium ions in the small intestine is important for the absorption of glucose, which is the physiologic basis for treating diarrhea by oral administration of saline solutions containing glucose. Bacterial toxins, for example, from *Clostridium difficile* or from *Escherichia coli*, can stimulate the chloride-bicarbonate ion exchange mechanism, resulting in life-threatening diarrhea consisting of loss of sodium, bicarbonate, and an isosmotic equivalent of water.

Colon

The functions of the colon are absorption of water and electrolytes from the chyme and storage of feces. A test meal reaches the cecum in approximately 4 hours and then passes slowly through the colon during the next 6 to 12 hours, during which time 1 to 2 L of chyme are converted to 200 to 250 g of feces ([Figure 32.10](#)). The circular muscle of the colon constricts and, at the same time, strips of longitudinal muscle (tinea coli) contract, causing the unstimulated portion of the colon to bulge outward into baglike sacs, or haustra. Vagal stimulation causes segmental contractions of the proximal part of the colon and stimulation of the pelvic nerves causes explosive movements. Activation of the sympathetic nervous system inhibits colonic activity. Bacteria are predictably present in the colon.

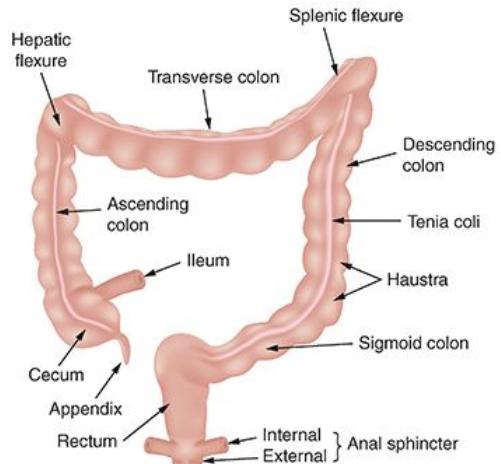


FIGURE 32.10 Anatomy of the colon.

Secretions of the Colon

Epithelial cells lining the colon secrete almost exclusively mucus, which protects the intestinal mucosa against trauma. The alkalinity of the mucus due to the presence of large amounts of bicarbonate ions provides a barrier to keep acids that are formed in the feces from attacking the intestinal wall. Irritation of a segment of colon as occurs with bacterial infection causes the mucosa to secrete large quantities of water and electrolytes in addition to mucus, diluting the irritating factors and causing rapid movement of feces toward the anus. The resulting diarrhea may result in dehydration and cardiovascular collapse.

Pancreas

The pancreas lies parallel to and beneath the stomach, serving as both an endocrine (insulin or glucagon) and exocrine gland. Exocrine secretions (approximately 1.5 L daily) are rich in bicarbonate ions to neutralize duodenal contents and digestive enzymes to initiate breakdown of carbohydrates, proteins, and fats.

Regulation of Pancreatic Secretions

Pancreatic secretions are regulated more by hormonal than neural mechanisms. For example, secretin is released by duodenal mucosa in response to hydrochloric acid. This hormone enters the circulation and causes the pancreas to produce large amounts of alkaline fluid necessary to neutralize the acidic pH of gastric fluid. In addition to the release of secretions, the presence of food in the duodenum causes the release of a second polypeptide hormone, cholecystokinin. Cholecystokinin also enters the circulation and causes the pancreas to secrete digestive enzymes (trypsin, amylase, lipases). Trypsins are activated in the gastrointestinal tract by the enzyme enterokinase, which is secreted by the gastrointestinal mucosa when chyme is exposed to the mucosa. Damage to the pancreas or blockade of a pancreatic duct may cause pooling of proteolytic enzymes, resulting in acute pancreatitis due to autodigestion by these enzymes. In general, pancreatic secretions are stimulated by the parasympathetic nervous system and inhibited by the sympathetic nervous system.

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Metabolism

Michael J. Murray

One of the most important functions of the gastrointestinal tract is the ingestion of nutrients—carbohydrate, protein, lipid, minerals, vitamins, and water—used for production of energy, creation of complex proteins and lipid moieties, and maintenance of electrolytes and total body water stores. The production of energy involves the oxidation of nutrients (carbohydrates, fats, and proteins) that results in creation of high-energy phosphate compounds in which energy is stored for life processes, with carbon dioxide and water produced as side products. The most important high-energy phosphate molecule is adenosine triphosphate (ATP) ([Figure 33.1](#)). This ubiquitous molecule is the energy storehouse for the body, providing the energy necessary for essentially all physiologic processes and chemical reactions. Probably the most important intracellular process that requires energy from hydrolysis of ATP is formation of peptide linkages between amino acids during protein synthesis. Likewise, efficient skeletal muscle contraction cannot occur without energy derived from ATP hydrolysis. Metabolism of nutrients is necessary for creation of ATP that, when hydrolyzed provides energy for transport of ions across cell membranes. Active transport is required to maintain the distribution of ions necessary for multiple cellular processes, including the propagation of nerve impulses. In renal tubules, as much as 80% of ATP is used for membrane transport of ions. In addition to its function in energy transfer, ATP is also the precursor of cyclic adenosine monophosphate, an important signaling molecule.

For adults, total energy expenditure averages 39 kcal/kg in men and 34 kcal/kg in women. Approximately 20 kcal/kg is expended as basal metabolism necessary to maintain integrity of the cell membrane and other energy-requiring tasks essential for life. In the resting state, the basal expenditure of calories is equivalent to approximately 1.1 kcal per minute, which requires approximately 200 to 250 mL per minute of oxygen in a 70-kg person for oxidation of nutrients. As the level of activities increase above the basal state, the caloric (and oxygen) requirements increase in proportion to the energy expenditure required ([Table 33.1](#)). The caloric values of carbohydrates, fats, and proteins are approximately 3.75, 9.3, and 4.1 kcal/g, respectively. Fat is the major energy storage depot because of its greater mass and high caloric value ([Figure 33.2](#)).¹ As a consequence, the primary form in which potential chemical energy is stored in the body is in adipose tissue as triglycerides. The high caloric density and hydrophobic nature of triglycerides permit efficient energy storage without adverse osmotic consequences.

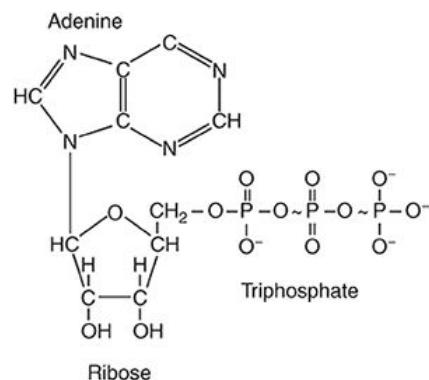


FIGURE 33.1 Metabolism of nutrients in cells is directed toward the ultimate synthesis of adenosine triphosphate. Energy necessary for physiologic processes and chemical reactions is derived from the high-energy phosphate bonds of adenosine triphosphate.

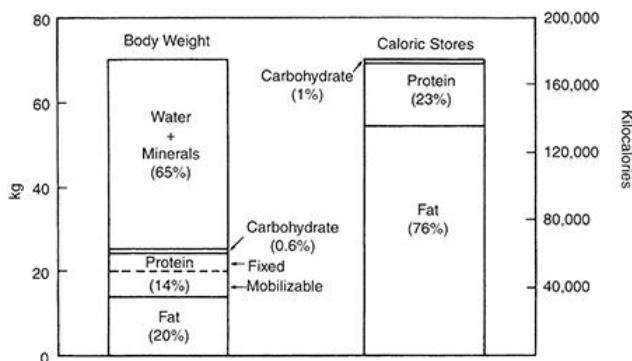


FIGURE 33.2 Comparison of the composition of body weight to caloric stores. From Berne RM, Levy MN, Koeppen BM, et al. Physiology. 5th ed. St Louis, MO: Mosby; 2004. Reprinted with permission from Bruce M. Koeppen, MD.

TABLE 33.1

Estimates of energy expenditure in adults

Activity	Calorie expenditure (kcal per minute)
Basal	1.1
Sitting	1.8
Walking (2.5 miles per hour)	4.3
Walking (4 miles per hour)	8.2
Climbing stairs	9.0
Swimming	10.9
Bicycling (13 miles per hour)	11.1

Carbohydrate Metabolism

Carbohydrates comprise a group of organic compounds that include sugars and starches and, in addition to carbon, contain hydrogen and oxygen in the same ratio as in water (2:1). Three disaccharides are important in human biology—sucrose: glucose and fructose; lactose: glucose and galactose; and maltose: glucose and glucose. Starch, found in grains such as wheat, rice, barley, and other plants, including potatoes and corn, consists of many units of glucose joined by glycosidic bonds. The monosaccharide glucose is an important energy source for the body and the sole source of energy for the brain.

Glucose levels are tightly controlled in the body by the enzyme glucose kinase. This enzyme is produced in the pancreas where it is involved in the rate-limiting step for the release of insulin and in the liver where it is involved in glycogenesis when intrahepatic concentration of glucose is high, for example, after a meal when glucose concentration in the portal vein is increased.¹

Ingested sugars and starches are digested in the small intestine to the monosaccharides glucose, fructose, and galactose. The latter two molecules can be converted to glucose in the liver; at least 99% of all the energy derived from glucose is used by mitochondria to form ATP in cells ([Figure 33.3](#)).

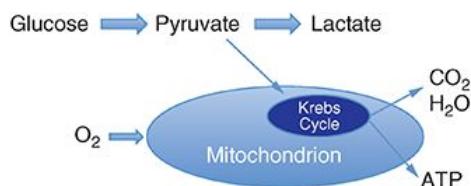


FIGURE 33.3 Formation of adenosine triphosphate (ATP) from glucose.

After absorption into the portal venous system, and when they reach the liver, monosaccharides form reversible complexes with membrane bound carrier proteins. The latter are coupled cotransporters; that is, the transport of these monosaccharides into cells is coupled to the transport of Na^+ .² Once inside hepatocytes, they are phosphorylated. For example, glucose is converted to glucose-6-phosphate under the influence of the enzyme hexose kinase. Phosphorylated glucose is ionized at a pH of 7, and because plasma membranes are not permeable to the ions, the phosphorylated glucose cannot pass back through the membrane and is effectively trapped within the cell.

In the liver, glucose can be stored as glycogen (see the following text) or released into the systemic circulation depending on blood glucose concentrations. Fructose, 2.5 times sweeter than glucose, has a much slower rate of absorption from the gastrointestinal tract and therefore has a glycemic index (measure of the increase in blood glucose of a carbohydrate, with glucose having a glycemic index of 100) of 23.³ The glycemic index of sucrose is 65; of lactose (glucose and galactose) is 46, the latter reflecting the fact that ingested galactose has very little effect on blood glucose levels.³

The fetus derives almost all its energy from glucose obtained from the maternal circulation. Immediately after birth, the infant stores of glycogen are sufficient to supply glucose for only a few hours. Furthermore, gluconeogenesis is limited in the neonate. As a result, the neonate is vulnerable to hypoglycemia if feeding is not initiated.

Glycogen

After entering cells, glucose can be used immediately for release of energy to cells or it can serve as a substrate for glycogen synthase, primarily in hepatocytes and myocytes. Glycogen synthase is activated when dephosphorylated by a protein phosphatase 1 (in the liver hepatic protein phosphatase 1 regulatory subunit 3B is the responsible phosphatase⁴), which in turn is regulated by insulin and glucagon. Activated glycogen synthase combines molecules of glucose into a long polymer, similar to the way plants store carbohydrate as starch. Glycogen synthase is deactivated when it is phosphorylated—by glycogen synthase kinase-3,5'-adenosine monophosphate-activated protein kinase, and protein kinase A. The liver and skeletal muscles are particularly capable of storing large amounts of glycogen, but all cells can store at least some glucose as glycogen, and the glycogen in these cells is increasingly recognized as having important roles in both health and disease. In hepatocytes, for example, if glycogen stores are high, fructose, for example, does not further increase glycogen stores but, especially if an individual is sedentary, is converted to very-low-density lipoprotein and released into the systemic circulation,⁵ hence, the current controversy over consumption of soft drinks and juices containing sucrose; 12 oz of some soft drinks have 35 g. However, during glycogen-depleting exercise, fructose-containing foods/drinks may optimize performance and recovery.⁵

The liver stores glycogen for release of glucose during fasting, and muscle, which can store as much as 90% of the glucose contained in a meal, catabolizes glycogen during strenuous exercise.⁶ The ability to form glycogen makes it possible to store substantial quantities of glucose without significantly altering the osmotic pressure of intracellular fluids. Glucose is cleaved from glycogen between meals, during fasting, and during exercise by glycogen phosphorylase and by a debranching enzyme.

Gluconeogenesis

Gluconeogenesis is the formation of glucose from amino acids and the glycerol portion of fat. Amino acids are first deaminated before entering the citric acid (Krebs) cycle (see [Figure 33.3](#)). This process occurs when body stores of glycogen decrease below normal levels. An estimated 60% of the amino acids in the body's proteins can be converted easily to pyruvate and glucose, whereas the remaining 40% have chemical configurations that make this conversion difficult.

Gluconeogenesis is stimulated by hypoglycemia. Particularly in the liver, simultaneous release of cortisol mobilizes proteins, making them available for breakdown to amino acids used in gluconeogenesis. Thyroxine is also capable of increasing the rate of gluconeogenesis.

[Energy Release From Glucose](#)

Glucose is progressively broken down into two molecules of pyruvate, both of which can enter the citric acid cycle ([Figure 33.4](#)), and the resulting energy is used to form ATP. For each mole of glucose that is completely degraded to carbon dioxide and water, a total of 38 moles of ATP is ultimately formed. The most important means by which energy is released from the glucose molecule is by glycolysis and the subsequent oxidation of the end products of glycolysis. Glycolysis is the splitting of the glucose molecule into two molecules of pyruvate, which enter the mitochondria where the pyruvate is converted to acetyl-coenzyme A (acetyl-CoA), which enters the citric acid cycle and is converted to carbon dioxide and hydrogen ions with the formation of ATP (oxidative phosphorylation). Oxidative phosphorylation occurs only in mitochondria, in the presence of adequate amounts of oxygen, and in the presence of a high ratio of ionized nicotinamide adenine dinucleotide to nicotinamide adenine dinucleotide and hydrogen.¹

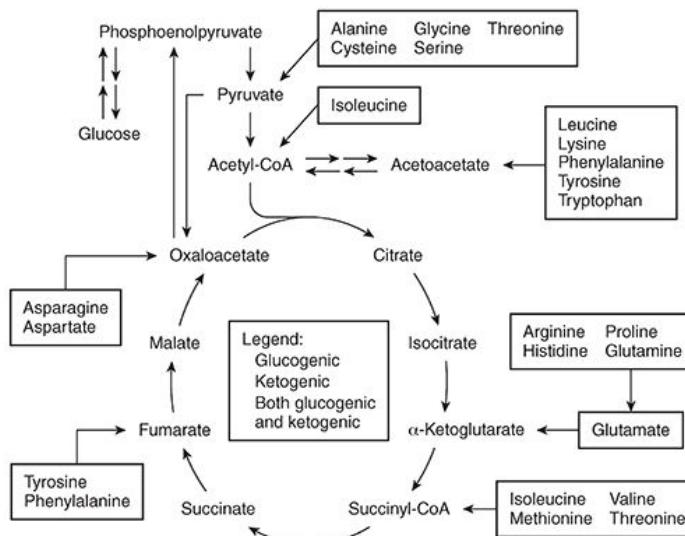


FIGURE 33.4 The citric acid cycle. Abbreviation: CoA, coenzyme A. *From Mikael Häggström, MD, Wikimedia Commons.*

Anaerobic Glycolysis

In the absence of adequate amounts of oxygen, a small amount of energy can be released by anaerobic glycolysis, also known as fermentation in plants, fungi, and bacteria because conversion of glucose to pyruvate does not require oxygen. Indeed, glucose is the only nutrient that can serve as a substrate for the formation of ATP without oxygen. This release of energy to cells can be lifesaving for a few minutes should oxygen become unavailable.

During anaerobic glycolysis, most pyruvic acid is converted to lactic acid, which diffuses rapidly out of cells into extracellular fluid. When oxygen is again available, lactic acid can be reconverted to glucose, predominantly in the liver. Severe liver disease may interfere with the ability of the liver to convert lactic acid to glucose, leading to metabolic acidosis.

Lipid Metabolism

Lipids are hydrophobic organic molecules that include waxes, sterols, fat-soluble vitamins, triglycerides (fats), phospholipids, and other substances. Lipids contain a high amount of potential energy but are also important as structural components of cell membranes, in signaling pathways, and as precursors to a number of cytokines. Fatty acids and their derivatives as well as molecules that contain sterols such as cholesterol are also considered lipids. Although there are biosynthetic pathways to synthesize and degrade lipids, some fatty acids are essential and must be ingested in the diet. Fatty acids are carboxylic acids consisting of a long hydrocarbon chain ending in a carboxyl group; the hydrocarbon chain can be saturated or unsaturated ([Figure 33.5](#)). Humans can desaturate carbon atoms no closer than the ninth carbon from the tail of the aliphatic

chain. However, humans require fatty acids (that are therefore essential) that are desaturated as close as the sixth and as close as the third carbon to the terminus of the aliphatic chain— ω 6 and ω 3 fatty acids, respectively. Twenty carbon chain fatty acids are stored in the second position of phospholipids (see the following text) and, when released, serve as substrates for a group of very important cytokines, the eicosanoids—prostaglandins, thromboxanes, and leukotrienes. Arachidonic acid (see [Figure 33.5](#)), a 20-carbon chain v6 fatty acid (C20:4 ω 6), is a precursor for prostaglandins and thromboxanes of the two series and leukotrienes of the four series, whereas eicosapentaenoic acid, C20:5 ω 3, is a precursor for prostaglandins and thromboxanes of the three series and leukotrienes of the five series.

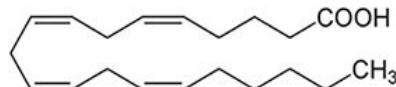


FIGURE 33.5 A long chain fatty acid, arachidonic acid. *From Yikrazuul via Wikimedia Commons.*

A glycerol stem to which three fatty acid molecules are bound is known as a triglyceride ([Figure 33.6](#)). A triglyceride molecule to which one of the terminal fatty acids is replaced with a phosphate ion is known as a phospholipid ([Figure 33.7](#)). Phospholipids are the building blocks of cell membranes ([Figure 33.8](#)), form myelin, and, because of their unique structure and functions, are being used in other scientific applications.

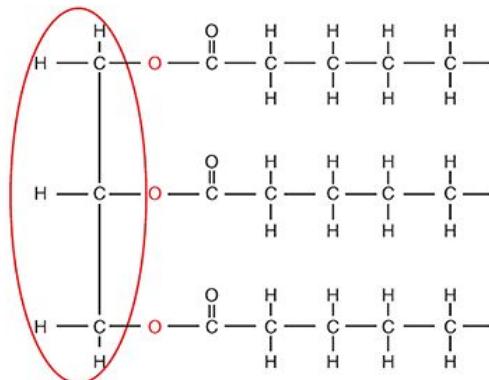


FIGURE 33.6 Triglyceride made up of a molecule of glycerol (circled in red) and three fatty acids.

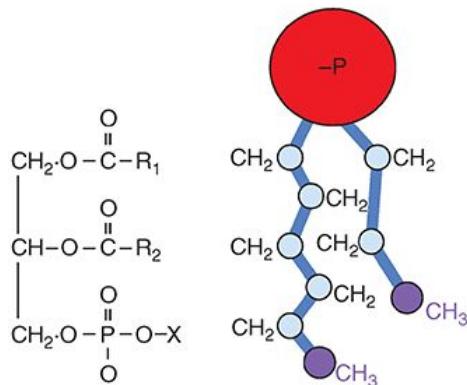


FIGURE 33.7 Substitution of one of the terminal fatty acids with a phosphate ion creates a phospholipid. Chemical structure on left; cartoon on right shows the hydrophilic phosphate group in red, with the hydrophobic hydrocarbon chains in blue. *From Wikimedia Commons.*

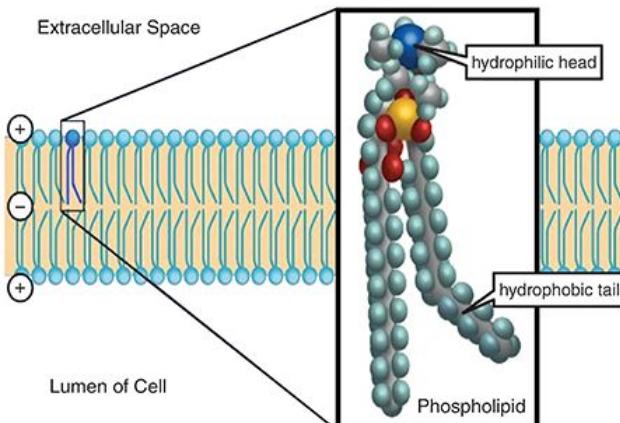


FIGURE 33.8 Cell membrane is a bilipid layer—made up of two opposing layers of phospholipids. The phosphate terminus is hydrophilic, whereas the two fatty acids, which are hydrophobic, orient to the interior of the membrane. *From Ties van Brusse, Wikimedia Commons.*

Triglycerides, after absorption from the gastrointestinal tract, are transported in the lymph and then, by way of the thoracic duct, into the circulation in droplets known as **chylomicrons**. Chylomicrons are rapidly removed from the circulation and stored as they pass through capillaries of adipose tissue and skeletal muscles. Triglycerides are used in the body mainly to provide energy for metabolic processes similar to those fueled by carbohydrates.

Cholesterol does not contain fatty acids, but it is a lipid because it is composed of carbon and hydrogen, not as aliphatic chains of carbon but with four rings made up of carbon ([Figure 33.9](#)). Seventy-five percent of cholesterol is produced in the liver in a synthetic process that involves 37 steps; the other 25% of cholesterol is ingested in the diet.

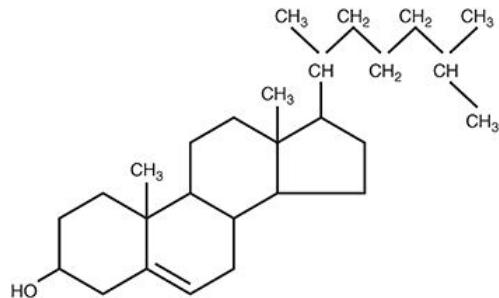


FIGURE 33.9 The chemical structure of a cholesterol molecule.

Molecules that are part lipid and part protein, lipoproteins, are also synthesized primarily in the liver ([Table 33.2](#)). The presumed function of lipoproteins is to provide a mechanism of transport for lipids throughout the body. Lipoproteins are classified according to their density, which is inversely proportional to their lipid content. All the cholesterol in plasma is found in lipoprotein complexes, with low-density lipoproteins (LDLs) representing the major cholesterol component in plasma. These LDLs provide cholesterol to tissues, where it is an essential component of cell membranes and is used in the synthesis of corticosteroids and sex hormones. In the liver, LDLs are taken up by receptor-mediated endocytosis. An intrinsic feedback control system increases the endogenous production of cholesterol when exogenous intake is decreased, explaining the relatively modest lowering effect on plasma cholesterol concentrations produced by low-cholesterol diets. If this endogenous increase in cholesterol synthesis is blocked by drugs that inhibit hydroxymethylglutaryl CoA reductase, then there is an appreciable decrease in the plasma cholesterol concentration.

TABLE 33.2

Types of proteins		
Globular	Fibrous	Conjugated
Albumin	Collagen	Mucoprotein
Globulin	Elastin fibers	Structural components of cells
Fibrinogen	Keratin	
Hemoglobin	Actin	
Enzymes	Myosin	
Nucleoproteins		

Drugs that selectively inhibit hydroxymethylglutaryl CoA are known as statins. Statins effectively lower plasma LDL cholesterol concentrations and may provide protection against acute cardiac events, perhaps reflecting antiinflammatory effects. In addition, statins lower plasma triglyceride concentrations and modestly increase high-density lipoprotein cholesterol concentrations. Drugs that bind bile salts (cholestyramine, colestipol) prevent cholesterol from reentering the circulation as part of the enterohepatic circulation. A disadvantage of using drugs that bind bile salts to lower plasma cholesterol concentrations is an associated increase in plasma triglyceride concentrations.

The first step in the use of triglycerides for energy is hydrolysis into fatty acids and glycerol and subsequent transport of these products to tissues, where they are oxidized. Almost all cells, except for brain cells, can use fatty acids interchangeably with glucose for energy. Degradation and oxidation of fatty acids occur only in mitochondria, resulting in progressive release of two carbon fragments (β -oxidation) in the form of acetyl-CoA (Figure 33.10). These acetyl-CoA molecules enter the citric acid cycle in the same manner as acetyl-CoA formed from pyruvate during the metabolism of glucose, ultimately leading to formation of ATP. In the liver, two molecules of acetyl-CoA formed from the degradation of fatty acids can combine to form acetoacetic acid (see Figure 33.10). A substantial amount of acetoacetic acid is converted to β -hydroxybutyric acid and small amounts of acetone. In the absence of adequate carbohydrate metabolism (starvation or uncontrolled diabetes mellitus), large quantities of acetoacetic acid, β -hydroxybutyric acid, and acetone accumulate in the blood to produce ketosis because almost all the energy of the body must come from metabolism of lipids. Whereas β -hydroxybutyric acid may be elevated in diabetic ketoacidosis in type 1 diabetes mellitus, an elevated level of α -hydroxybutyric acid is highly correlated with impaired glucose tolerance and may serve as a biomarker for type 2 diabetes mellitus.⁸

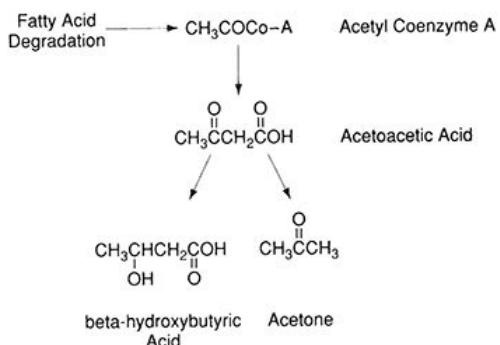


FIGURE 33.10 Fatty acid degradation in the liver leads to the formation of acetyl-coenzyme A (acetyl-CoA). Two molecules of acetyl-CoA combine to form acetoacetic acid, which, in large part, is converted to β -hydroxybutyric acid and, in lesser amounts, to acetone.

In contrast to glycogen, large amounts of lipids can be stored in adipose tissue and in the liver. A major function of adipose tissue is to store triglycerides until they are needed for energy. Epinephrine and norepinephrine activate triglyceride lipase in cells, leading to mobilization of fatty acids.

Protein Metabolism

Approximately 75% of the solid constituents of the body are proteins ([Table 33.3](#)). All proteins are composed of the same 20 amino acids, and several of these must be supplied in the diet because they cannot be formed endogenously (essential amino acids) ([Table 33.4](#)). Dietary proteins must be cleaved into amino acids and di- and tripeptides before they can be absorbed. The process begins in the stomach where pepsinogen is converted to pepsin in the acidic pH. The process continues in small intestine into which the pancreas secretes trypsin and chymotrypsin and carboxypeptidases. These gastric and pancreatic proteases hydrolyze proteins into medium- and small-chain peptides. Peptidases in the brush border of the small intestine hydrolyze these medium- and small-chain peptides into free amino acids and di- and tripeptides. These end products of digestion, formed on the surface of the enterocyte, are ready for absorption by sodium-dependent amino acid transporters.

TABLE 33.3

Composition of lipids in the plasma

	Phospholipid (%)	Triglyceride (%)	Free cholesterol (%)	Cholesterol esters	Protein (%)	Density
Chylomicrons	3	90	2	3	2	0.94
LDL	21	6	7	46	20	1.019-1.063
HDL	25	5	4	16	50	1.063-1.21
IDL	20	40	5	25	10	1.006-1.019
VLDL	17	55	4	18	8	0.94-1.006

Abbreviations: HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein.

TABLE 33.4

Amino acids

Essential	Nonessential
Arginine	Alanine
Histidine	Asparagine
Isoleucine	Aspartic acid
Leucine	Cysteine
Lysine	Glutamic acid
Methionine	Glutamine
Phenylalanine	Glycine
Threonine	Proline
Tryptophan	Serine
Valine	Tyrosine

Nonessential amino acids can be synthesized from the appropriate α -keto acid. For example, pyruvate formed during the glycolytic breakdown of glucose is the keto acid precursor of alanine. Each amino acid has an acidic carboxyl group (COOH) and an amino group (NH_3^+) ([Figure 33.11](#)). Proteins are formed by amino acids connected one to another by an amide bond, a covalent chemical bond between the carboxyl group of one amino acid with the amino group of another amino acid. The resulting $\text{C}(\text{O})\text{NH}$ bond is called a peptide bond, and the resulting molecule is an amide. The four-atom functional group $-\text{C}(=\text{O})\text{NH}-$ is called a peptide link ([Figure 33.12](#)). Even the smallest proteins characteristically contain more than 20 amino acids connected by peptide linkages, whereas complex proteins have as many as 100,000 amino acids. In addition, more than

one amino acid chain in a protein may be bound to another amino acid chain by hydrogen bonds, hydrophobic bonds, or electrostatic forces.

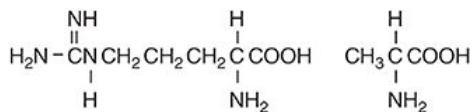


FIGURE 33.11 Examples of amino acids containing an acidic group (COOH) or an amino group (NH_2)



FIGURE 33.12 Formation of amides from carboxylic acid and primary amine

Amino acids are relatively strong acids and exist in the blood principally in the ionized form. After a meal, the blood amino acid concentration increases only a few milligrams, reflecting rapid tissue uptake, especially by the liver. Passage of amino acids into cells requires active transport mechanisms because these substances are too large to pass by diffusion or through channels in cell membranes. In proximal renal tubules, amino acids that have entered the glomerular filtrate are actively transported back into the blood. These transport mechanisms have maximums above which amino acids appear in the urine. In the normal person, however, loss of amino acids in the urine each day is negligible. Failure to transport amino acids into the blood is indicative of renal disease.

Storage of Amino Acids

Immediately after entry into cells, amino acids are conjugated under the influence of intracellular enzymes into cellular proteins. The concentration of amino acids within cells is low as the cell uses them as substrate to create proteins within the liver, kidneys, and gastrointestinal mucosa. Nevertheless, these proteins can be rapidly decomposed again into amino acids under the influence of intracellular lysosomal digestive enzymes. The resulting amino acids can then be transported out of cells into blood to maintain optimal plasma amino acid concentrations. Tissues can synthesize new proteins from amino acids in blood. This response is especially apparent in relation to protein synthesis in cancer cells. Cancer cells are prolific users of amino acids, and, simultaneously, the proteins of other tissues become markedly depleted, contributing to cachexia.

Plasma Proteins

Plasma proteins are represented by (1) albumin, which provides colloid osmotic pressure; (2) globulins necessary for innate and acquired immunity; and (3) fibrinogen, which polymerizes into long fibrin threads during coagulation of blood. Essentially, all plasma albumin and fibrinogen and 60% to 80% of the globulins are formed in the liver. Additional globulins are formed in lymphoid tissues and other cells of the reticuloendothelial system. The rate of plasma protein formation by the liver can be greatly increased in situations, such as severe burns, in which there is loss of large amounts of fluid and protein.

The hepatic synthetic rate of proteins depends on the concentration of amino acids in the portal vein and in the hepatic artery. Even during starvation or severe debilitating diseases, the ratio of total tissue proteins to total plasma proteins in the body remains relatively constant at approximately 33:1. Because of the reversible equilibrium between plasma proteins and other proteins of the body, one of the most effective of all therapies for acute protein deficiency is the intravenous administration of plasma proteins. Within hours, amino acids of the administered protein become distributed throughout cells of the body to form proteins where they are needed.

Albumin

Albumin is the most abundant plasma protein and is principally responsible for maintaining plasma osmotic pressure and as a transporter of plasma-bound substances, often including exogenously administered drugs. Normal daily synthesis of albumin is about 10 g, and the half-life for this protein may be as long as 22 days. Therefore, serum albumin concentrations may not be noticeably decreased in early states of acute hepatic failure. However, within hours of the onset of a critical illness or injury, albumin levels decrease by as much as 33% due to changes in the distribution between intravascular and extravascular compartments and rates of synthesis and degradation of protein. Despite the fact that low serum albumin is a poor prognostic factor in critical illness, supplementation has not been shown to improve prognosis.

Coagulation Factors

Hepatocytes synthesize all coagulation factors with the exception of von Willebrand factor and factor VIIIC. Coagulation may be rapidly impaired by acute liver failure, reflecting the short plasma half-life for many critical components (factor VII: 100-300 minutes). Vitamin K (uptake dependent on bile salts) is necessary for modification of several of the clotting factors (prothrombin, antithrombin, protein S, and protein C) and may be deficient in malabsorptive states and malnutrition.

Use of Proteins for Energy

Once cells contain a maximum amount of amino acids, any additional amino acids are deaminated (oxidative deamination) to keto acids that can enter the citric acid cycle to become ATP or the keto acids are released into the bloodstream, taken up by adipocytes, and converted to and stored as triglycerides. Ammonia resulting from deamination is converted to urea in the liver for excretion by the kidneys. Acute hepatic failure manifests by accumulation of toxic concentrations of ammonia. Certain deaminated amino acids are similar to the breakdown products that result from glucose and fatty acid metabolism. For example, deaminated alanine is pyruvic acid, which can be converted to glucose or glycogen, or it can be converted to acetyl-CoA, which is polymerized to fatty acids. The conversion of amino acids to glucose or glycogen is **gluconeogenesis**, and the conversion of amino acids into fatty acids is **ketogenesis**. In the absence of protein intake, approximately 20 to 30 g of endogenous protein are degraded into amino acids daily. In severe starvation, cellular functions deteriorate because of protein depletion. Carbohydrates and lipids spare protein stores to a certain extent because they are used in preference but not exclusively to proteins for energy.

Growth hormone and insulin promote the synthetic rate of cellular proteins, possibly by facilitating the transfer of amino acids into cells. Glucocorticoids increase the breakdown rate of extrahepatic proteins, thereby making increased amino acids available to the liver. This allows the liver to synthesize increased amounts of cellular proteins and plasma proteins. Testosterone increases protein deposition in tissues, particularly the contractile proteins of skeletal muscles.

Effects of Stress on Metabolism

Carbohydrate, lipid, and protein metabolism are significantly altered by stress. In response to stress, the body increases secretion of cortisol, catecholamines, and glucagon, resulting in increased endogenous glucose production (hepatic gluconeogenesis) and hyperglycemia (to provide glucose to cells for ATP production in those cells involved in the fight or flight response). Stress-induced β -adrenergic stimulation increases the breakdown of triglycerides (lipolysis). The products of lipolysis can be used for gluconeogenesis or directly by cells to produce ATP. Likewise, a predictable response to stress is catabolism of proteins in skeletal muscles, releasing keto acids that can be used for ATP production or for gluconeogenesis.

Exogenous glucose administered to injured or septic patients has a minimal effect on gluconeogenesis and lipolysis. Conversely, administration of glucose in the presence of starvation decreases gluconeogenesis and lipolysis.

Obesity

Given the importance of energy stores to individual survival and reproductive capacity, the ability to conserve energy in the form of adipose tissue at one time may have conferred a survival advantage; however, an increase in adiposity would have been a disadvantage in that it increased the risk of predation.⁹ Independent

of the teleologic rationale, the combination of easy access to calorically dense foods and a sedentary lifestyle¹⁰ has made the metabolic consequences maladaptive. In addition, certain medications are commonly associated with weight gain ([Table 33.5](#)).

TABLE 33.5

Drugs commonly associated with weight gain

Classification	Drug	Alternative drug
Antidepressants	Tricyclic antidepressants Monoamine oxidase inhibitors	Selective serotonin reuptake inhibitors
Antidiabetics	Insulin Sulfonylureas Thiazolidinediones	Metformin Acarbose
Antiepileptics	Gabapentin Valproic acid	Lamotrigine Topiramate
Antipsychotics	Clozapine	Haloperidol
Steroids	Glucocorticoids	

Obesity is the most common and costly nutritional problem in the United States. Based on body mass index (BMI) (weight in kilograms divided by the square of the height in meters), 67% of adult males and 62% of adult females are overweight (BMI ≥ 25) and 27.5% of adult males and 34% of adult females (BMI ≥ 30 to <40) are obese; individuals with BMI ≥ 40 have extreme obesity. The prevalence of obesity peaks between 60 and 69 years of age, but greater numbers of children are increasingly found to be obese for their age.¹¹

For every 5-unit increase in BMI above 25 kg/m^2 , mortality increases by ~29%, mortality from vascular disease by ~40%, and diabetes-related mortality by >200%. Central adiposity, that is, increased waist circumference, correlates with cardiometabolic risk, independent of the BMI.¹² In this regard, an overweight person with a predominant abdominal fat distribution (common in elderly males with impaired glucose tolerance) may be at high risk for these diseases even if not considered obese by BMI criteria. The increased risk for morbidity and mortality extend beyond measurements of BMI and fat distribution, as reflected by the diagnosis of **metabolic syndrome**, which is present if a patient has three of the following five risk factors: increased waist circumference (as described previously), low levels of high-density lipoprotein cholesterol, increased triglycerides, hypertension, and glucose intolerance ([Table 33.6](#)). The risk of anesthesia may be increased in obese patients, reflecting mechanical difficulties (airway, positioning, and ventilation) and increased incidence of comorbid conditions (diabetes mellitus, systemic hypertension).

TABLE 33.6

Criteria for diagnosis of metabolic syndrome (any three of the following characteristics)

Characteristic	Specific finding
Waist circumference	Males $>102 \text{ cm}$ (40 inches) Females $>88 \text{ cm}$ (35 inches)
Blood glucose concentration (fasting)	$>110 \text{ mg/dL}$
Increased systemic blood pressure	Systolic $>130 \text{ mm Hg}$ Diastolic $>85 \text{ mm Hg}$
Serum triglyceride concentration	$>150 \text{ mg/dL}$
High-density lipoprotein cholesterol concentration	Males $<40 \text{ mg/dL}$ Females $<50 \text{ mg/dL}$

Treatment of obesity by decreasing caloric intake and increasing metabolic rate (exercise) directed toward a long-term decrease in body weight is largely ineffective, unless coupled with an intensive

counseling program.¹³ Proteins and carbohydrates can be metabolically converted to fat, and there is no evidence that changing the relative proportions of protein, carbohydrate, and fat in the diet without decreasing caloric intake will promote weight loss. However, fat has a higher caloric density than protein and carbohydrate, and its contribution to the palatability of foods promotes its ingestion and increases the intake of calories.

Pharmacologic Treatment

A number of U.S. Food and Drug Administration–approved drugs are available for treating obesity, all with varying efficacy and side effects. Phentermine, a sympathomimetic amine, is an appetite suppressant that is used for short-term (a few weeks) therapy intended to induce weight loss. Only a fraction of a pound per week is lost, and its use is associated with an increase in systemic blood pressure, heart rate, and anxiety.¹⁴ It is the most commonly prescribed weight loss drug in the United States. In the past, this drug was frequently used in combination with fenfluramine (the latter induces the development of valvular heart disease, similar to that seen with carcinoid syndrome and has been removed from the market.). It has been replaced by another combination drug, phentermine and topiramate, which is also somewhat effective. Along with the side effects associated with phentermine, the addition of topiramate may induce dry mouth, paresthesia, constipation, dysgeusia, insomnia, and impaired cognition.¹⁴

Orlistat inhibits lipases in the gastrointestinal lumen, thus antagonizing triglyceride hydrolysis and decreasing fat absorption by about 30%. Because orlistat is not absorbed, its ability to cause weight loss likely reflects the resulting low-fat diet and lower caloric intake. Weight loss with orlistat is modest, a mean of 2.5 to 3.4 kg. Gastrointestinal side effects (abdominal discomfort, flatus, fecal urgency) reflecting the increased fat content in stool are dose limiting and occur in the majority of patients treated with orlistat. Orlistat should not be prescribed for patients with known malabsorptive conditions, and daily multivitamin supplementation is recommended.¹⁴

Lorcaserin is a third drug currently used in the United States, associated with a mean weight loss of 3.1 kg over 1 year compared to a placebo. Lorcaserin is a selective 5-HT_{2C} agonist, which activates proopiomelanocortin production and promotes weight loss through satiety.¹⁴

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Antiemetics*

Updated by: Christopher M. Lam • Michael J. Murray

Postoperative nausea and vomiting (PONV) is defined as nausea and/or vomiting occurring within 24 to 48 hours of surgery. Along with pain, PONV is the most important complaint patients report following surgery under anesthesia and is the leading cause of unanticipated hospital admission following outpatient surgery.^{1,2} It is a very common complication; without prophylaxis, nausea occurs in up to 40% of patients who undergo general anesthesia but can be as high as 80% in high-risk patients.¹ There have been hundreds of studies examining ways to prevent PONV and to effectively treat it when it does develop. Anesthesia societies and organizations continue to develop guidelines on how to best address the problem, the most recent by the Society for Ambulatory Surgery in 2016.³ There have been a number of nonpharmacologic methods used to prevent and/or attenuate this disorder,^{4,5} but this chapter focuses on the pharmacologic therapies used as prophylaxis and treatment of PONV.

Definition

Postoperative nausea and vomiting (PONV), recognized by the National Library of Medicine as a single medical subject heading term, actually refers to two distinct entities. Although nausea and emesis are intimately related, a person can have one without the other. Some drugs are more effective in treating one than the other. A patient who experiences nausea or has emesis within 24 to 48 hours of a surgical procedure that required anesthesia meets the criteria for the diagnosis of PONV. The classification is further divided into early PONV (within 24 hours of emergence from anesthesia) or late PONV (24-48 hours, sometimes even up to 72 hours after the procedure), also called postdischarge nausea and vomiting.⁶

Incidence

As mentioned previously, PONV occurs in 30% to 40% of all patients who undergo general anesthesia, but among patients with identified risk factors for developing PONV, it can occur in 70% to 80%. From a patient satisfaction point of view, PONV is a major issue. The Perception of Quality in Anesthesia questionnaire was developed by addressing concerns from 120 patients and community members. Seven hundred and fourteen patients were surveyed, revealing PONV, postoperative pain, and communication with the anesthesia provider being the most important aspect of the patient experience.⁷ Independent of patient perception, PONV has been associated with physical morbidity, including dehydration, electrolyte abnormalities, wound dehiscence, bleeding, esophageal rupture, and airway compromise.⁸

Pathophysiology

Patients with nausea have a subjective feeling of the need to vomit; the sensation is very, very unpleasant. Emesis is not always preceded by nausea. Vomiting typically begins with contractions of the ileum and jejunum, moving their contents back toward the stomach. The glottis is then closed, protecting the airway, and the diaphragm contracts, creating negative intrathoracic pressure as the pharyngeal sphincters relax. At the same time, the abdominal muscles contract, creating increased intra-abdominal pressure that compresses the stomach. Under pressure and with open upper sphincters, emesis occurs. When the stomach is empty, retching or dry heaves occur, which involves the same process happens, but no stomach contents are expelled. Emesis is different from regurgitation in which the sphincters are not completely closed and the stomach contents can pass into the esophagus in the setting of elevated abdominal pressure such as might occur during excessive mask ventilation.

The highly choreographed sequence that occurs during vomiting and retching is controlled by the vomiting center. It consists of the nucleus of the tractus solitarius and parts of the reticular formation in the

medulla oblongata.⁹ A number of neurotransmitters activate and inhibit activity of the vomiting center, including acetylcholine, dopamine, histamine, substance P, and serotonin ([Figure 34.1](#)). Drugs that are used to control nausea and vomiting modulate the activity of these receptors. The chemoreceptor trigger zone (CRTZ) located in the area postrema on the floor of the fourth ventricle is outside the blood–brain barrier. As such, a natural hormone or potentially dangerous substance does not need to cross the blood–brain barrier to be detected by the CRTZ.

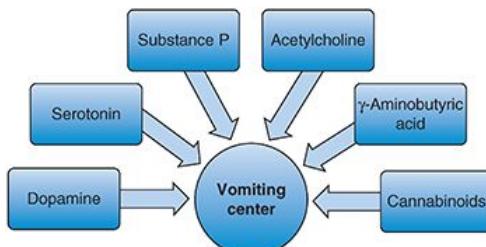


FIGURE 34.1 Pharmacologic systems that interact with the vomiting center.

The vomiting center can be activated by the vestibular apparatus, the thalamus and cerebral cortex, and neurons within the gastrointestinal tract itself. The interaction with the vestibular apparatus could create the common interaction between vertigo and vomiting whereas the cerebral cortex could induce psychogenic vomiting.

Upon activation, the vomiting center sends efferent signals via the cranial nerves V, VII, IX, X, and XII through the vagal parasympathetic fibers and sympathetic chain and to skeletal muscle through α motor neurons.¹⁰ Signals from the vomiting center via these nerves trigger the complex motor process resulting in emesis.

Prophylaxis

Preventing PONV is easier than treating it,¹¹ but the side effects of the antiemetic drugs are such that the American Society of Anesthesiologists has recommended that antiemetic agents should be used for the prevention and treatment of nausea and vomiting when indicated but not routinely. To determine whether prophylaxis is indicated, it is important to assess a patient's propensity to develop PONV according to risk factors that increase or decrease a patient's chances of experiencing PONV. First validated by Apfel et al¹² in 1999, these risk factors are traditionally divided into patient, surgical, and anesthetic risk factors.

Patient Factors

Women, nonsmokers, and those with a history of motion sickness¹³ or of previous episodes of PONV are at an increased risk for experiencing PONV if they undergo a surgical procedure under anesthesia. Women most likely are at increased risk for PONV because of the effects of progesterone and/or estrogen on the CRTZ or on the vomiting center itself, as evidenced by the fact that the incidence of PONV varies within the menstrual cycle and is reduced after menopause.¹⁴ Obese patients, because of exposure to greater amount of emetogenic lipophilic drugs such as the inhalational anesthetic agents stored in their adipose tissue, were once thought to have a higher incidence of PONV, but a subsequent investigation did not show this to be true.³ Other patient factors that have been disproven or hold limited clinical relevance for PONV risk include history of anxiety, history of migraine, perioperative fasting, presence of nasogastric tube, and use of supplemental oxygen.³ Generally, the incidence of PONV decreases per decade in adults, whereas the incidence increases with age in children, with relatively low incidence reported in children younger than 3 years of age.¹⁵

Surgical Factors

The longer the surgical procedure, the greater the risk for a patient to develop PONV, potentially due to prolonged exposure to emetogenic lipophilic drugs.¹⁶ Independent of duration, certain surgical procedures have been associated with an increased incidence of PONV, including laparotomies; gynecologic operations;

laparoscopic procedures; as well as ear, nose, throat, breast, plastic, and orthopedic surgical procedures.¹⁶ In pediatric patients having surgery under general anesthesia, the greatest association is with the surgical procedure itself. Herniorrhaphy, tonsillectomy and adenoidectomy, strabismus procedures, and surgical procedures on male genitalia have the highest risk.¹⁷

Anesthetic Factors

There have been a number of anesthetic-related factors that investigators have assessed for their relationship to the development of PONV. The inhalation anesthetic agents, nitrous oxide, neostigmine, and opioids have all been implicated in the genesis of PONV.¹⁵ However, correlation is limited, and most scoring systems used to identify patients at risk for PONV do not incorporate anesthetic factors, although the duration of anesthetic exposure is associated with the development of PONV.³ Furthermore, although the use of intraoperative opioids does not appear to increase the risk of PONV, postoperative opioids do.¹⁸

Pharmacologic Interventions

A multimodal approach for prophylaxis in patients at high risk for developing PONV and for rescue therapy in patients who develop PONV in the postanesthetic care unit works well because of the complexity of systems involved in the pathogenesis of PONV. The drugs that modulate activity in the vomiting center and CRTZ are listed in **Table 34.1** and discussed in the following sections. Traditionally, there are six categories of medications used to treat PONV (serotonergic antagonists, anticholinergics, antihistamines, corticosteroids, dopamine antagonists, and neurokinin-1 antagonists); however, other medications have been successful in comanagement of this condition, including benzodiazepines and cannabinoids.

TABLE 34.1
Pharmacologic therapies for treatment of nausea and vomiting

5-HT ₃ antagonists	Dolasetron Granisetron Ondansetron Palonosetron Ramosetron Tropisetron
Anticholinergics	Atropine Hyoscine Scopolamine
Antihistamines	Dimenhydrinate Diphenhydramine Meclizine Promethazine
Benzodiazepines	Midazolam
Cannabinoids	Dronabinol Nabilone
Corticosteroids	Dexamethasone
Dopamine (D ₂) antagonists	Amisulpride Chlorpromazine Droperidol Haloperidol Metoclopramide Prochlorperazine
Neurokinin-1 antagonists	Aprepitant Fosaprepitant

5-HT₃ Receptor Antagonists

The 5-HT₃ receptors are excitatory ligand-gated nonselective cation channels. The ion channel is a pentamer consisting of five subunits, each with four transmembrane segments that form a central pore, which can be readily permeated by small cations.¹⁹ The 5-HT₃ receptors are extensively distributed on neurons in the gastrointestinal tract and in the brain. Serotonin is released from the enterochromaffin cells of the small intestine, stimulates the vagal afferents through 5-HT₃ receptors, and initiates the vomiting reflex. The highest density of 5-HT₃ receptors in the brain is found in the area postrema, the site of the CRTZ.¹⁹ Antagonists of these receptors have antiemetic effects. Clinically used 5-HT₃ receptor antagonists are selective for these receptors with almost no significant binding with other 5-HT receptor subtypes.

Clinical Uses

The 5-HT₃ receptor antagonists (ondansetron, tropisetron, granisetron, dolasetron) represent a significant advance in the prophylaxis and treatment of nausea and vomiting are useful antiemetics in the prophylaxis and treatment of chemotherapy (CINV) and radiation therapy-induced nausea and vomiting²⁰ and are equally effective in the prevention and treatment of PONV. The 5-HT₃ receptor antagonists, however, are not effective in the treatment of nausea and vomiting caused by vestibular stimulation (see the following text). The convenience of use, efficacy, and safety profile account for the popularity of 5-HT₃ receptor antagonists for management of PONV.

Comparison With Other Antiemetics

Ondansetron (4 mg), dexamethasone (4 mg), or droperidol (1.25 mg) administered intravenously (IV) as prophylactic therapy before induction of general anesthesia are equally effective in decreasing the incidence of PONV by about 26%.¹⁸ However, a cost–benefit analysis did not support the use of 5-HT₃ receptor antagonists for routine antiemetic prophylaxis when studied in the early 2000s,²¹ but now that some 5-HT₃ antagonists are available as lower-cost generic preparations, they are deemed the “gold standard” for antiemetics.³

Pharmacokinetics

The 5-HT₃ receptor antagonists are readily absorbed after oral administration and readily cross the blood–brain barrier. Following IV administration, the maximum brain concentration is achieved quickly. These antagonists are moderately bound to protein (60%–75%). Metabolism is by different subtypes of cytochrome P450 enzymes, and the metabolites undergo principally renal excretion. The bioavailability of ondansetron, granisetron, and dolasetron range from 56% to 77% with the t_{1/2} between 3.5 and 7.3 hours. Given the similar safety and therapeutic profiles of these drugs, their pharmacokinetics do not play a role in the selection of 5-HT₃ antagonists when not combined with other antiemetics.²²

Ondansetron

Ondansetron is a carbazalone derivative that is structurally related to serotonin and possesses specific 5-HT₃ subtype receptor antagonist properties without altering dopamine, histamine, adrenergic, or cholinergic receptor activity.²³ As a result, ondansetron is free of neurologic side effects common to droperidol and metoclopramide.²³ Ondansetron is effective when administered orally or IV and has an oral bioavailability of about 60% with therapeutic blood concentrations appearing 30 to 60 minutes after administration. Like other 5-HT₃ antagonists described in the following text, metabolism to inactive metabolites occurs predominantly in the liver, and the elimination half-time is 3 to 4 hours. The most commonly reported side effects from treatment with ondansetron are headache and diarrhea. Transient increases in the plasma concentrations of liver transaminase enzymes have been observed only in patients receiving chemotherapy and may be due to these drugs rather than ondansetron. Cardiac arrhythmias and conduction disturbances (atrioventricular block) have been reported after the IV coadministration of ondansetron and metoclopramide.²⁴ Ondansetron

and other 5-HT₃ receptor antagonists can cause slight prolongation of the QTc interval on the electrocardiogram of treated patients, but this has not created the same level of concern as that ascribed to droperidol for unclear reasons.

It is estimated that for every 100 patients who receive ondansetron for the prevention of PONV, 20 patients will not vomit who would have vomited without treatment (“number needed to treat”), and 3 of those 100 patients will develop a headache who would have not had this adverse effect without the drug (“number needed to harm”).²⁵ Ondansetron, 4 to 8 mg IV (administered over 2-5 minutes immediately before the induction of anesthesia), is highly effective in decreasing the incidence of PONV in a susceptible patient population (ambulatory gynecologic surgery, middle ear surgery). Oral (0.15 mg/kg) or IV (0.05-0.15 mg/kg) administration of ondansetron is effective in decreasing the incidence of postoperative vomiting in preadolescent children undergoing ambulatory surgery, including tonsillectomy and strabismus surgery.

Ondansetron, although highly effective in decreasing the incidence and intensity of PONV, does not totally eliminate this complication. The most significant feature of ondansetron prophylaxis and treatment is the relative freedom from side effects as compared with other described classes of antiemetic drugs. Use of propofol for induction and maintenance of anesthesia is almost as effective as ondansetron in preventing PONV (19% vs 26%, respectively), and ondansetron continues to have antiemetic effects when used in a propofol-based anesthetic.¹⁸

Tropisetron

Tropisetron is an indoleacetic acid ester of tropine that possesses highly selective 5-HT₃ receptor blocking effects. Compared with ondansetron, tropisetron has the benefit of a longer elimination half-time (7.3 vs 3.5 hours). Overall, the beneficial effects and side effects of tropisetron resemble those of ondansetron.²⁰ This drug is also effective in the treatment of symptoms related to carcinoid syndrome and may also possess gastrokinetic properties. As an antiemetic, tropisetron is effective in prevention of chemotherapy- and radiotherapy-induced emesis and in the prevention of PONV when administered (2-5 mg IV) before the induction of general anesthesia.²⁰ Rescue treatment using a single dose of tropisetron is often effective in decreasing further nausea and vomiting. Tropisetron did not prevent PONV associated with epidural morphine, whereas dexamethasone (5 mg IV) was effective.²⁰ However, tropisetron is not approved for use in the United States.³

Granisetron

Granisetron is a more selective 5-HT₃ receptor antagonist than ondansetron. Like ondansetron, granisetron is effective when administered orally and IV. Doses as low as 0.02 to 0.04 mg/kg IV have been described as effective in prevention of emesis and prevention of PONV.²⁶ Concomitant administration of dexamethasone significantly improved the acute antiemetic efficacy of granisetron.²⁷ Metabolism to inactive metabolites occurs in the liver with only about 10% of the drug excreted unchanged by the kidneys. The elimination half-time of granisetron (9 hours) is 2.5 times longer than that of ondansetron and thus may require less frequent dosing. For example, a single dose of granisetron may be effective for 24 hours. The longer duration of action is particularly beneficial in outpatient surgery where nausea and vomiting commonly occur on the way home. Side effects are mild and include headache, sedation, and diarrhea.

Dolasetron

Dolasetron is a highly potent and selective 5-HT₃ receptor antagonist that is effective in the prevention of CINV and PONV following either oral or IV administration. Dolasetron is a prodrug. After its administration, dolasetron is rapidly metabolized to hydrodolasetron, which is responsible for the antiemetic effect.²⁸ Hydrodolasetron has an elimination half-time of approximately 8 hours and is approximately 100 times more potent as a serotonin antagonist than the parent compound.

A single IV dose of dolasetron, 1.8 mg, is equivalent to ondansetron, 32 mg IV, and granisetron, 3 mg IV, in preventing CINV. Established PONV is effectively blunted by treatment with dolasetron, 12.5 mg IV.²⁶ Oral dolasetron, 25 to 50 mg, is effective as prophylaxis for decreasing PONV. Although serotonergic

pathways are involved in the development of postoperative shivering, dolasetron was not effective in preventing this complication.²⁹ Common side effects include headache, dizziness, and increased appetite. It is unclear if an increased heart rate attributed to dolasetron is different from the incidence observed in placebo-treated patients.²⁶ In 2010, the U.S. Food and Drug Administration (FDA) advised against use of IV dolasetron for CINV due to concerns for QT prolongation and torsades de pointes; however, it can still be used for PONV treatment due to lower doses used.³⁰

Anticholinergics

Muscarinic acetylcholine receptors are found in the vestibular system near the CRTZ. Activation of this receptor results in activation of the CRTZ resulting in nausea. Anticholinergics prevent this pathway resulting in its antiemetic effects.³¹ One of the most commonly used perioperative anticholinergic antiemetic is scopolamine.

Scopolamine

Prevention of Motion-Induced Nausea and of PONV

Transdermal absorption of scopolamine provides sustained therapeutic plasma concentrations, which protect against motion-induced nausea usually without introducing prohibitive side effects such as sedation, cycloplegia, or drying of secretions. For example, a postauricular application of scopolamine delivers the drug at about 5 µg per hour for 72 hours (total absorbed dose is <0.5 mg). Once the patch is removed, the half-life is 9 hours.²⁶ Protection against motion-induced nausea is greatest if the transdermal application of scopolamine is initiated at least 4 hours before the noxious stimulus. Administration of transdermal scopolamine (TDS) after the onset of symptoms is less effective than prophylactic administration. Similar protection against motion-induced nausea by oral or IV administration of scopolamine would require large doses, resulting in undesirable side effects and subsequent poor patient acceptance.

Application of a TDS patch has been shown to exert significant antiemetic effects in patients experiencing motion sickness and in those treated with patient-controlled analgesia or epidural morphine for the management of postoperative pain.³² It is well known that motion sickness is caused by stimulation of the vestibular apparatus. It has also been shown that morphine and synthetic opioids increase vestibular sensitivity to motion.³³ It is presumed that scopolamine blocks transmission to the medulla of impulses arising from overstimulation of the vestibular apparatus of the inner ear. Indeed, application of a TDS patch before the induction of anesthesia protects against nausea and vomiting after middle ear surgery, which is likely due to altered function of the vestibular apparatus.³² Furthermore, prophylactic TDS applied the evening before surgery decreases but does not abolish the occurrence of nausea and vomiting after outpatient laparoscopy using general anesthesia.³² Conversely, not all reports describe an antiemetic effect in patients treated with TDS who are undergoing general anesthesia.³⁴ Apfel et al³² performed a meta-analysis of 25 studies of TDS used to treat PONV and found that TDS was associated with significant reductions in PONV with both early and late application during the first 24 hours after the start of anesthesia. The TDS was associated with a higher prevalence of visual disturbances at 24 to 48 hours after surgery, but no other adverse events were noted.³² Some of the visual disturbances may be due to anisocoria, which has been attributed to contamination of the eye after digital manipulation of the TDS patch.²⁶ More than 90% of unilateral dilated pupils occur on the same side as the patch. This diagnosis is confirmed by history and failure of the mydriasis to respond to topical installation of pilocarpine.

Central Anticholinergic Syndrome

Scopolamine and atropine can enter the central nervous system (CNS) and produce symptoms characterized as the central anticholinergic syndrome. Symptoms range from restlessness and hallucinations to somnolence and unconsciousness. Presumably, these responses reflect blockade of muscarinic cholinergic receptors and competitive inhibition of the effects of acetylcholine in the CNS.³⁵ Glycopyrrolate does not easily cross the blood-brain barrier and thus is not likely to cause central anticholinergic syndrome.

Central anticholinergic syndrome has been attributed to the IV administration of anticholinergic drugs before the induction of anesthesia.³⁵ Physostigmine, a lipid-soluble tertiary amine anticholinesterase drug administered in doses of 15 to 60 µg/kg IV, is a specific treatment for the central anticholinergic syndrome. Treatment may need to be repeated every 1 to 2 hours. Edrophonium, neostigmine, and pyridostigmine are not effective antidotes because their quaternary ammonium structure prevents these drugs from easily entering the CNS. The central anticholinergic syndrome is often mistaken for delayed recovery from anesthesia. Ventilation may be depressed. Differentiation of this syndrome from other causes of perioperative confusion is possible with slow IV administration of physostigmine, 0.4 mg/kg.³⁶

Overdose

Deliberate or accidental overdose with an anticholinergic drug produces a rapid onset of symptoms characteristic of muscarinic cholinergic receptor blockade. The mouth becomes dry, swallowing and talking are difficult, vision is blurred, photophobia is present, and tachycardia is prominent. The skin is dry and flushed, and a rash may appear, especially over the face, neck, and upper chest (blush area).³⁷ Even therapeutic doses of anticholinergic drugs sometimes may selectively dilate cutaneous vessels in the blush area. Body temperature is likely to be increased by anticholinergic drugs, especially when the environmental temperature is also increased. This increase in body temperature largely reflects inhibition of sweating by anticholinergic drugs, emphasizing that innervation of sweat glands is by sympathetic nervous system nerves that release acetylcholine as the neurotransmitter.³⁷ Small children are particularly vulnerable to drug-induced increases in body temperature, with “atropine fever” occurring occasionally in this age group after administration of even a therapeutic dose of anticholinergic drug. Minute ventilation may be slightly increased due to CNS stimulation and the impact of an increased physiologic dead space due to bronchodilation. Arterial blood gases are usually unchanged. Fatal events due to an overdose of an anticholinergic drug include seizures, coma, and medullary ventilatory center paralysis.

Small children and infants seem particularly vulnerable to developing life-threatening symptoms after an overdose with an anticholinergic drug. Physostigmine, administered in doses of 15 to 60 µg/kg IV, is the specific treatment for reversal of symptoms.³⁸ Because physostigmine is metabolized rapidly, repeated doses of this anticholinesterase drug may be necessary to prevent the recurrence of symptoms.

Decreased Barrier Pressure

Barrier pressure is the difference between gastric pressure and lower esophageal sphincter pressure. Administration of atropine, 0.6 mg IV, or glycopyrrolate, 0.2 to 0.3 mg IV, decreases lower esophageal sphincter pressure and thus decreases barrier pressure and the inherent resistance to reflux of acidic fluid into the esophagus.³⁹ This effect may persist longer with glycopyrrolate (60 minutes) than after administration of atropine (40 minutes).

Histamine Receptor Antagonists

The effects of histamine are mediated via histaminergic receptors, and at least three histamine receptors subtypes have been identified and classified as H₁, H₂, and H₃.⁴⁰ Histamine acting through H₁ receptors and inositol phospholipid hydrolysis evokes smooth muscle contraction in the gastrointestinal tract. In the CNS, histamine receptors are present in the area postrema and vomiting center of the vestibular nucleus along with the nucleus tractus solitarius.^{26,41} As such, antihistamines have long been used for treatment and prevention of motion sickness.⁴² Nonspecific antihistamines, likely acting on H₁ receptors including diphenhydramine, dimenhydrinate, cyclizine, and promethazine, are used as antiemetics. It is important to note that many H₁ receptor antagonists have anticholinergic effects as well, concomitantly blocking muscarinic receptors in the vestibular system.^{26,41} The antiemetic properties may partially be attributed to this mechanism. Some H₂ receptor antagonists have been used for antiemetic effects with mixed results.²⁶

Dimenhydrinate has been used to treat PONV as well as motion sickness. It is speculated that the efficacy of dimenhydrinate in motion sickness and inner ear diseases may be due to inhibition of the integrative functioning of the vestibular nuclei by decreasing vestibular and visual input. Manipulation of the

extraocular muscles as in strabismus surgery may trigger an “oculo-emetic” reflex similar to the well-described oculocardiac reflex. If the afferent arc of this reflex is also dependent on the integrity of the vestibular nuclei apparatus, then dimenhydrinate may attenuate or block this reflex and decrease the incidence of PONV. Administration of dimenhydrinate, 1 mg/kg IV, in adults decreases vomiting after outpatient surgery.³ In children, antihistamines significantly decreases the incidence of vomiting after ophthalmologic surgery but not adenotonsillectomy.⁴³

Diphenhydramine is another commonly used antihistamine for PONV management. It is available in PO and IV administration (25–50 mg per dose via either route). Most antihistamines are extensively metabolized by the hepatic CYP system.²⁶ Patients with increased levels of hepatic CYP3A4 and CYP2D6 may have alterations in metabolic activity resulting in variances in therapeutic effect in patients when given antihistamines.²⁶ The most common side effects from antihistamines are associated to their anticholinergic effects including dry mouth and somnolence.

Corticosteroids

Dexamethasone has been shown to be useful in the management of PONV, but the mechanism of antiemetic activity is unclear. Corticosteroids are proposed to centrally inhibit prostaglandin synthesis and control endorphin release. It has also been theorized that the antiinflammatory effect of steroids along with the resultant decrease in arachidonic acid release plays a role.⁴⁴ As discussed already, dexamethasone has efficacy similar to ondansetron and droperidol¹⁸ and with a minimal side effect profile associated with one-time use. Obese and diabetic patients are at increased risk for perioperative hyperglycemia when they receive a single dose of dexamethasone.

Dopamine Receptor Antagonists

Along with serotonin and histamine, dopamine has a role in modulating the sensation of nausea in the CRTZ.⁴⁵ In total, there are five subtypes of the dopamine receptor, and the D₂ subtype is found in the CRTZ.⁴⁶ Among one of the four categories of antiemetics first used, dopamine D₂ antagonists were found from derivatives of phenothiazines. Domperidone was first identified in 1974 as a D₂ antagonist with inability to cross the blood–brain barrier with less chance to evoke extrapyramidal side effects, allowing for safer utilization as an antiemetic. Later, other commonly utilized antiemetics such as benzamides and butyrophenones were found to have D₂ antagonistic properties as well.⁴⁵ Here, we discuss these medications as they relate to their antidopaminergic properties.

Benzamides

Metoclopramide

The benzamides, aside from their antidopaminergic effects, stimulate the gastrointestinal tract via cholinergic mechanism, which results in (1) contraction of the lower esophageal sphincter and gastric fundus, (2) increased gastric and small intestinal motility, and (3) decreased muscle activity in the pylorus and duodenum when the stomach contracts. Metoclopramide and domperidone are the two benzamides currently in use, but domperidone is not available in the United States because the FDA was concerned about its use in lactating women (increases milk production), although the risk for prolonged QTc intervals risk was low for domperidone.^{47,48}

This review therefore focuses on metoclopramide, which presumably has either a peripheral effect as just described or because it readily crosses the blood–brain barrier may have direct effects on the CRTZ and/or vomiting center because of its antidopaminergic effect.

A meta-analysis of 30 trials evaluating 10 mg of systemic metoclopramide on PONV outcomes concluded that, compared to placebo, the incidence of 24-hour PONV was reduced with metoclopramide with an odds ratio of 0.58 and a 95% confidence interval of 0.43 to 0.78. The number needed to treat was 7.8.⁴⁹

Because of its antidopaminergic activity, metoclopramide should be used with caution if at all in patients with Parkinson disease, with restless legs syndrome, or who have movement disorders related to dopamine

inhibition or depletion.⁵⁰ In patients with no known movement disorders, dystonic extrapyramidal reactions (oculogyric crisis, opisthotonus, trismus, torticollis) occur in less than 1% of patients treated chronically with metoclopramide. Although usually a problem if large oral doses (40-80 mg daily) are administered chronically, there are reports of neurologic dysfunction related to the preoperative administration of metoclopramide.⁵¹ These extrapyramidal reactions are identical to the parkinsonism evoked by antipsychotic drugs that antagonize the CNS actions of dopamine.⁵² Akathisia, a feeling of unease and restlessness may follow the IV administration of metoclopramide, sometimes so severe that it can result in cancellation of surgery⁵³ or which may manifest in the postanesthesia care unit.⁵⁴

Butyrophенones

Butyrophenones are members of the first-generation antipsychotics that exercise their activity via antagonism of the dopamine receptor.⁵⁵ Aside from antidopaminergic effects, these medications also have antinoradrenergic, anticholinergic, and antihistaminergic activity.

Droperidol and Haloperidol

After the FDA placed boxed warnings on droperidol due to its association with prolonged QT syndromes, many physicians stopped using droperidol.⁵⁶ However, the FDA's warning on droperidol was based on case reports in which higher doses were used, higher than are necessary for the treatment of PONV. Because of its efficacy at low dose, the use of droperidol has increased over the last several years for prophylaxis and as rescue therapy as an antiemetic.⁵⁷ Prophylactic doses of droperidol of 0.625 to 1.25 mg IV are effective for the prevention and treatment of PONV. For patients in whom dopamine antagonism is not a concern, droperidol is as effective as dexamethasone or ondansetron in preventing and treating PONV.¹⁸

Haloperidol also has antiemetic properties when used in low doses, 0.5 to 2 mg IV. At these doses, sedation does not occur.

Phenothiazines

Phenothiazines are another group of medications with antidopaminergic activity used for their antiemetic effects. It is also another member of first-generation antipsychotics similar to the butyrophenones with antidopaminergic, antiadrenergic, and antihistaminergic activity.^{45,58} The most commonly used medication in this class is chlorpromazine with typical therapeutic dosing at 10 to 25 mg orally or 25 to 50 mg intramuscularly/IV.⁵⁹ Similar to the butyrophenones, side effects from phenothiazines include dry mouth, sedation, QTc prolongation, and extrapyramidal symptoms. However, phenothiazines may also cause agranulocytosis and orthostatic hypotension; thus, care should be exercised when providing this medication to patients as an antiemetic.⁵⁸

Amisulpride

Amisulpride is a selective D₂ and D₃ dopaminergic antagonist originally used as a second-generation antipsychotic for the management of schizophrenia.⁶⁰ Because of its antidopaminergic activity and safety profile, it was investigated for use as an antiemetic. A double-blind randomized control trial comparing amisulpride to placebo found that it was superior to placebo for management of PONV with no increased risk of QTc prolongation or extrapyramidal side effects.⁶¹ Zhang et al⁶² performed a meta-analysis resulting in five identified studies evaluating amisulpride's ability to prevent and treat PONV. The findings showed that low-dose amisulpride was safe and efficacious for prevention and treatment of PONV compared to placebo.⁶² Amisulpride was approved by the FDA in February 2020 for use in PONV management with the potential adverse effects of QTc prolongation, increased prolactin levels, hypokalemia, hypotension, abdominal distention, and infusion site pain.⁶³ The recommended dosage for prevention of PONV is 5 mg IV over 1 to 2 minutes at the time of induction of anesthesia, whereas the treatment dosage for PONV was 10 mg over 1 to 2 minutes.⁶⁴

Neurokinin-1 Antagonists

Neurokinin-1 is a centrally and peripherally expressed G-protein–coupled receptor whose primary ligand is substance P. The expression of neurokinin-1 in the brainstem is theorized to have a role in the vomiting reflex through the nucleus tractus solitarius and area postrema.⁶⁵ Neurokinin-1 antagonists are increasingly used for CINV as chemotherapeutic drugs induce substance P release resulting in acute and delayed nausea, which are both attenuated by these medications.⁶⁶ Their effectiveness in CINV patients led to their use in the perioperative management of PONV. Aprepitant and its prodrug fosaprepitant are the only FDA-approved neurokinin-1 antagonists.⁶⁵ Aprepitant is available only as an oral capsule with dosing of 40 mg within 3 hours of induction of anesthesia for prevention of PONV.⁶⁵ The expense of aprepitant has resulted in recommendations that it only be given to patients at high risk for PONV or in patients for whom vomiting would compromise the surgical repair.³ Common side effects of aprepitant include headache, fatigue, and constipation, with less common side effects including mucous inflammation, neutropenia, and fever. It is generally well tolerated at doses 40 mg or less. Because of aprepitant's effect on the P450 CYP3A4 enzyme, one should be cautious when administering this medication to patients who are concomitantly taking medications metabolized by this enzyme.⁶⁵

Midazolam

The activity of the benzodiazepines is relatively well known, but with respect to a possible mechanism of action in PONV, benzodiazepines may decrease synthesis and release of dopamine within the CRTZ.⁶⁷ Perioperative administration of midazolam may reduce PONV by 38% to 55%; administration of 2 mg of midazolam IV 30 minutes prior to the end of surgery may be as effective as 4 mg of ondansetron for the treatment of PONV.⁶⁸ A meta-analysis by Ahn et al⁶⁹ of 16 studies confirmed the effectiveness of midazolam for management of PONV.

Cannabinoids

Much like the neurokinin antagonists, cannabinoids have been found to be a useful adjunct in treating CINV.⁷⁰ The mechanism of their action is thought to be mediated by the binding of cannabinoid receptor type 1 peripherally (suppressing intestinal motility) and centrally in the nucleus of the solitary tract.²⁶ Currently, the orally available cannabinoids are nabilone (a synthetic analogue of Δ-9-tetrahydrocannabinol) and dronabinol (synthetic Δ-9-tetrahydrocannabinol).²⁶ Despite their success in treating CINV, cannabinoids are ineffective for managing PONV.³

Summary

PONV presents a significant and prevalent condition for patients in the perioperative setting. Because of the physiologic consequences and increased risks of comorbidities with burden to the health care system of PONV, measures to mitigate and treat this condition should be initiated when possible. Currently, six classifications of medications are used to treat this condition. Weighing patient comorbidities and factors, will allow for careful selection of an appropriate agents.

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Antacids and Gastrointestinal Motility Drugs*

Updated by: Michael J. Murray

Aspiration is the inhalation of gastric or oropharyngeal contents into the lungs. Aspiration during general anesthesia occurs in approximately 1 in 8,500 adults and 1 in 4,400 children younger than 16 years of age.¹ A study of 102,425 pediatric cases published in 2016 identified 22 patients who had an anesthetic and who aspirated, an incidence of 0.02% (1 in 4,655), similar to what had been reported 10 years earlier.² Most of the patients were American Society of Anesthesiologists (ASA) 1 and 2 with no history of previous aspiration, which makes identifying patients at risk difficult. As in previous studies, aspiration was unexpected and occurred more commonly in ASA 1E and 2E patients during induction of anesthesia. A systematic review of 35 articles reporting on aspiration during sedation (conscious or monitored anesthesia care) for procedures found few cases except during gastrointestinal endoscopy, with full recovery typical. Of those that occurred outside of gastrointestinal endoscopy suites, most were benign.³ However, there were eight deaths in the 292 patients who aspirated during gastrointestinal endoscopy, a mortality rate of 2.7%. An examination of the records of 60,770 patients who underwent upper gastrointestinal endoscopies identified 28 cases (1 in 2,170) who aspirated. Those who aspirated were more likely to be admitted to an intensive care unit, had longer hospital lengths of stay, and had a higher mortality rate (0% vs 7%; $P = .004$).⁴

Factors associated with pulmonary complications of aspiration include the volume and acidity of the aspirated gastric contents. Drugs that increase the pH of gastric contents (antacids) and that decrease the volume of gastric contents (prokinetic drugs) have a role in decreasing the severity of the sequelae of aspirating gastric contents. Enforcement of the recently updated ASA Task Force fasting recommendations may also reduce the risk of pulmonary aspiration.⁵

Oral Antacids

Antacids are drugs that neutralize hydrogen ions from gastric contents or decrease the secretion of hydrogen chloride into the stomach. Oral antacids have been used for centuries. In current practice, the oral antacids used most often are salts of magnesium, calcium, and aluminum; the hydrogen ions in stomach acid react with the base, forming a stable compound. As hydrogen ions are consumed, the pH of the stomach contents increases. The best known example would be sodium bicarbonate, which, in the stomach, combines with hydrochloric acid (HCl) to produce sodium chloride (NaCl), water (H₂O), and carbon dioxide (CO₂).

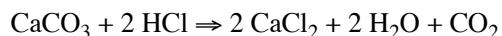
Increasing gastric pH relieves the symptoms of gastritis, but if the pH of the stomach is too high, digestion of food is inhibited as an acidic pH is necessary for the breakdown of many foods. In addition, increases in gastric fluid pH to >5 result in inactivation of pepsin and produce bile-chelating effects. Neutralization of gastric fluid pH increases gastric motility via the action of gastrin (aluminum hydroxide is an exception) and increases lower esophageal sphincter tone by a mechanism that is independent of gastrin.

Sodium bicarbonate results in a prompt and rapid antacid action, so much so that the pH is raised to the point that the stomach's pH is neutral, which can lead to acid rebound. Recently published data show that reducing hydrogen ion concentration in the stomach affects acid-base balance in such a way that it increases the performance of trained cyclists⁶ and enhances the recovery of elite boxers after a strenuous workout.⁷ Patients with hypertension or heart disease, though, may not tolerate the increased sodium load associated with chronic use of this antacid.

Magnesium hydroxide (or magnesium oxide, which in an aqueous medium as found in the stomach promptly forms magnesium oxide) also produces prompt neutralization of gastric acid but is not associated with significant acid rebound. A prominent laxative effect (osmotic diarrhea) is characteristic of magnesium hydroxide. Approximately, 15% of the magnesium is absorbed,⁸ enough that some clinicians prescribe it to

treat hypomagnesemia, but also enough, depending on the oral dose, to cause neurologic, neuromuscular, and cardiovascular impairment in patients with renal dysfunction. Long-term use of magnesium-containing antacids is associated with hip fractures in older patients.⁹

Calcium carbonate, CaCO₃, is also used as an antacid.

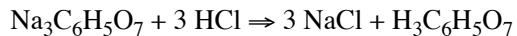


The plasma concentration of calcium is increased transiently. Symptomatic hypercalcemia may occur in patients with renal disease. The administration of calcium carbonate-containing antacids may result in hypophosphatemia. Even small amounts of calcium carbonate-containing antacids evoke hypersecretion of hydrogen ions (acid rebound). The chalky taste of calcium carbonate is an additional disadvantage. The release of CO₂ in the stomach may cause eructation and flatulence. Constipation is minimized by including magnesium oxide with calcium carbonate.

Aluminum hydroxide [Al(OH)₃] in the stomach dissociates into aluminum (Al₃) and OH⁻, which then binds to hydrogen (H⁺) to produce H₂O, and the Al³⁺ binds to anions, primarily Cl⁻, to form insoluble salts. Less than 1% of the available aluminum is absorbed and then excreted by the kidneys; in patients with renal disease, the plasma and tissue concentrations of Al³⁺ may become excessive. Side effects of Al(OH)₃ include hypomagnesemia, hypophosphatemia, anemia, and constipation.¹⁰ Seizures and encephalopathy in patients undergoing hemodialysis have been attributed to intoxication with aluminum. A number of neurodegenerative diseases are associated with the administration of Al(OH)₃.¹¹ Aluminum compounds, in contrast to other antacids, cause slowing of gastric emptying and marked constipation and, therefore, are occasionally prescribed for patients with chronic diarrhea for its constipating effect; however, hypophosphatemia may result.

Occasional failure of particulate antacids to increase gastric fluid pH may reflect inadequate mixing with stomach contents or an unusually large volume of gastric fluid such that the standard dose of antacid is inadequate to neutralize gastric H⁺ ions. Layering is also common with particulate antacids.

Sodium citrate (Na₃C₆H₅O₇) is a nonparticulate antacid.



There are no prospective studies that demonstrate that oral antacids decrease the risk of aspiration pneumonitis in patients having an anesthetic, but it is common practice to administer sodium citrate to pregnant patients and to nonpregnant patients who are at risk for aspirating and are undergoing an anesthetic.¹² Sodium citrate is preferred over other oral antacids because it is less likely to cause a foreign body reaction if aspirated and its mixing with gastric fluid is more complete and more rapid than is that of particulate antacids. Sodium citrate, 15 to 30 mL of a 0.3-mol/L solution administered 15 to 30 minutes before the induction of anesthesia, is effective in reliably increasing gastric fluid pH in pregnant¹³ and nonpregnant patients.

Complications of Antacid Therapy

The increase in gastric volume and in pH resulting from antacid use has been associated with adverse events. Chronic alkalinization of gastric fluid has been associated with bacterial overgrowth in the duodenum and small intestine.¹⁴ The use of antacids also can result in metabolic alkalosis,¹⁵ which in turn can lead to alkalinization of the urine, predisposing patients to urinary tract infections; if it is chronic, urolithiasis is possible. Increased urine pH may persist >24 hours after administration of an antacid, leading to changes in the renal elimination of drugs.

Acid rebound is a side effect that is unique to calcium-containing antacids. This response is characterized by a marked increase in gastric acid secretion that takes place several hours after neutralization of gastric acid. It is unclear if acid rebound persists with chronic calcium carbonate treatment.

The milk-alkali syndrome is characterized by hypercalcemia, increased blood urea nitrogen and plasma creatinine concentrations, and systemic alkalosis, as reflected by an above-normal plasma pH. The plasma calcium-phosphate concentration is usually increased and renal function, with calcification of the parenchyma, may be markedly decreased.¹⁶ This syndrome is most commonly associated with ingestion of large amounts of calcium carbonate along with >1 L of milk every day.¹⁵

Phosphorus depletion can occur in patients who ingest large doses of aluminum salts because, although chloride is the anion most commonly bound by Al³⁺, the aluminum cation will also bind phosphate or any other anion, depending on the concentration of the various anions in the stomach. This effect may actually be beneficial in patients with renal disease because it can decrease the plasma phosphate concentration, but, unfortunately, patients with chronic renal failure are at risk for developing toxicity from the aluminum. Individuals with hypophosphatemia may experience anorexia, skeletal muscle weakness, and malaise. Osteomalacia, osteoporosis, and fractures may occur. If it is necessary to administer aluminum-containing antacids on a chronic basis to patients with osteomalacia or osteoporosis, phosphate supplements should be considered.

Drug Interactions

Gastric alkalinization increases gastric emptying, resulting in a faster delivery of drugs into the small intestine. This may facilitate absorption of drugs that are poorly absorbed or it may shorten the time available for absorption, depending on where in the gastrointestinal tract absorption occurs. There are many drugs whose absorption is enhanced by antacids. The rate of absorption of salicylates, indomethacin, and naproxen is increased when gastric fluid pH is increased. Conversely, absorption of drugs that are weak bases, for example, ketoconazole, itraconazole, dipyridamole, and enoxacin, is decreased if gastric pH is >5.¹⁷

Aluminum hydroxide accelerates absorption and increases bioavailability of diazepam by an unknown mechanism. Conversely, bioavailability of certain drugs may be decreased because of their capacity to form complexes with antacids. Antacids containing aluminum, and to a lesser extent, calcium or magnesium, interfere with the absorption of tetracyclines and possibly digoxin from the gastrointestinal tract.

Histamine-Receptor Antagonists

Histamine induces contraction of smooth muscles in the airways, increases the secretion of acid in the stomach, and stimulates the release of neurotransmitters in the central nervous system (CNS) through three receptor subtypes: H₁, H₂, H₃. Recently, a fourth histamine receptor, designated as an H₄ receptor, was cloned, which has led to the development of several drugs that inhibit its action.

Depending on what responses to histamine are inhibited, drugs are classified as H₁-, H₂-, H₃-, and H₄-receptor antagonists. Histamine-receptor antagonists bind to receptors on effector cell membranes, to the exclusion of agonist molecules, without themselves activating the receptor. For histamine-receptor antagonists, this is a competitive and reversible interaction. Histamine-receptor antagonists do not inhibit release of histamine but, rather, attach to receptors and prevent responses mediated by histamine.

H₃- and H₄-receptor modulators do not currently play a role in anesthetic practice and as such are not described in detail.

H₁-Receptor Antagonists

H₁-receptor antagonists are characterized as first-generation and second-generation receptor antagonists (**Figure 35.1**). First-generation drugs tend to produce sedation, whereas second-generation drugs are relatively nonsedating (**Table 35.1**). H₁-receptor antagonists are highly selective for H₁ receptors, having little effect on H₂, H₃, or H₄ receptors. First-generation H₁-receptor antagonists may also activate muscarinic, cholinergic, 5-hydroxytryptamine (5-HT serotonin), or α-adrenergic receptors, whereas few of the second-generation antagonists have any of these properties. The selectivity of the second-generation antagonists for H₁ receptors decreases CNS toxicity. An increased understanding of the molecular pharmacologic features of these drugs has resulted in their reclassification as inverse agonists rather than as H₁-receptor antagonists.¹⁸

H_1 -receptor antagonists act as inverse agonists that combine with and stabilize the inactive form of the H_1 receptor, shifting the equilibrium toward the inactive state.

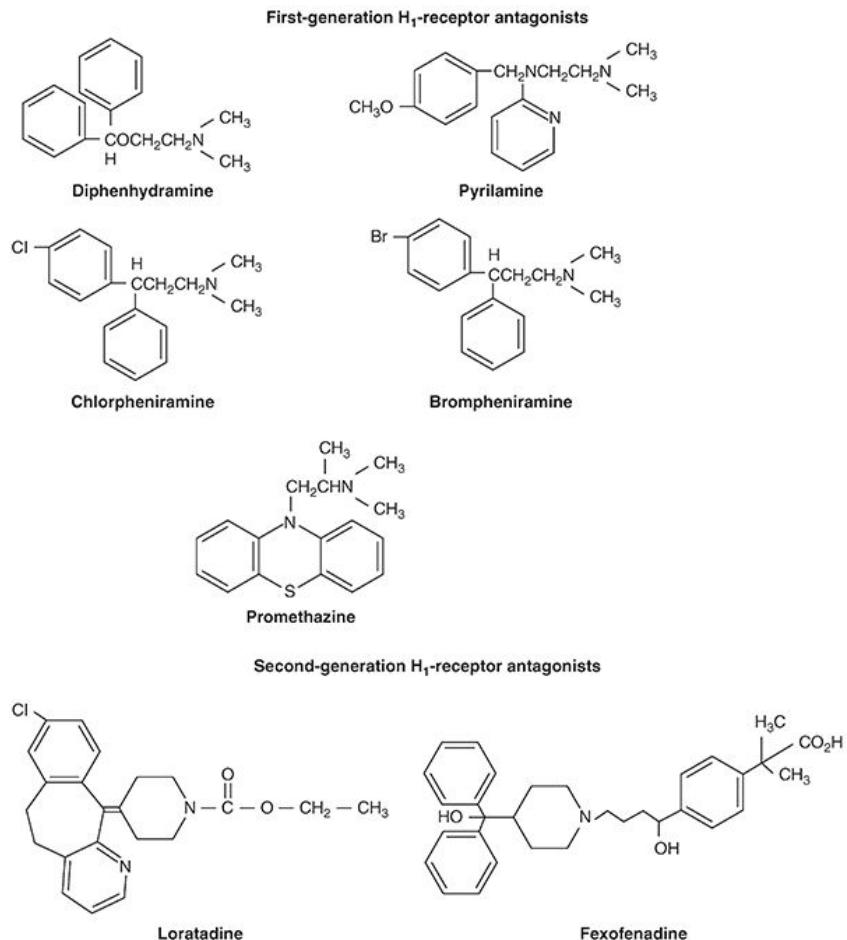


FIGURE 35.1 First- and second-generation H_1 -receptor antagonists.

TABLE 35.1

Pharmacokinetics of H_1 -receptor antagonists^a

	Time to peak plasma level (h)	Elimination half-time (h)	Clearance rate ($\text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)
First-generation receptor antagonists			
Chlorpheniramine	2.8	27.9	1.8
Diphenhydramine	1.7	9.2	23.3
Hydroxyzine	2.1	20.0	98
Second-generation receptor antagonists			
Loratadine	1.0	11.0	202
Acrivastine	0.85-1.4	1.4-2.1	4.56
Azelastine	5.3	22	8.5

^aData from Simons FE, Simons KJ. The pharmacology and use of H_1 -receptor-antagonist drugs. *N Engl J Med.* 1994;330:1663-1670.

Pharmacokinetics

H₁-receptor antagonists are well absorbed after oral administration, often reaching peak plasma concentrations within 2 hours (see [Table 35.1](#)). Many are highly protein bound, with ranges from 78% to 99%. Most of the new H₁-receptor antagonists do not accumulate in tissue to any extent. Interestingly, there is little tachyphylaxis seen with their use.¹⁹ Most H₁-receptor antagonists are metabolized by the hepatic microsomal mixed-function oxidase system. Plasma concentrations are relatively low after a single oral dose, which indicates first-pass hepatic extraction. Values for the elimination half-lives of these drugs are variable. For example, the elimination half-life of chlorpheniramine is >24 hours and that of acrivastine is about 2 hours (see [Table 35.1](#)). Acrivastine is excreted mostly unchanged in urine, as is cetirizine, the active carboxylic metabolite of hydroxyzine.

Clinical Uses

H₁-receptor antagonists are among the most widely used of all medications. H₁-receptor antagonists prevent and relieve the symptoms of allergic rhinoconjunctivitis (sneezing, nasal and ocular itching, rhinorrhea, tearing, and conjunctival erythema),²⁰ but they are less effective for the nasal congestion characteristic of a delayed allergic reaction. In contrast to their role in the treatment of allergic rhinitis, H₁-receptor antagonists provide little benefit in the treatment of upper respiratory tract infections and are of no benefit in the management of otitis media. Depending on the H₁-receptor antagonist selected and its dose, pretreatment may provide some protection against bronchospasm induced by various stimuli (histamine, exercise, cold dry air). Earlier concerns about drying of secretions in patients with asthma have not been substantiated. In patients with chronic urticaria, H₁-receptor antagonists relieve pruritus and decrease the number, size, and duration of urticarial lesions. In some patients with refractory urticaria, concurrent treatment with an H₂-receptor antagonist (cimetidine, ranitidine) may enhance relief of pruritus. In addition to a direct effect on H₂ receptors, which account for 10% to 15% of all histamine receptors in the vasculature, this effect may be due in part to the ability of some H₂-receptor antagonists to inhibit the metabolism of H₁-receptor antagonists by the hepatic cytochrome P450 system, leading to an increased plasma and tissue concentration of H₁-receptor antagonists. The second-generation H₁-receptor antagonists (cetirizine, fexofenadine, loratadine, desloratadine, azelastine) are supplanting first-generation drugs (diphenhydramine, chlorpheniramine, cyproheptadine) in the treatment of allergic rhinoconjunctivitis and chronic urticaria. Their greater cost can be justified because of a more favorable risk-benefit ratio (eg, they have fewer CNS side effects). For example, the first-generation H₁-receptor antagonists have sedating effects that result in delayed reaction times.

Diphenhydramine is prescribed as a sedative, an antipruritic, and an antiemetic. When administered alone, it modestly stimulates ventilation by augmenting the interaction of hypoxic and hypercarbic ventilatory drives. When diphenhydramine is administered in combination with systemic or neuraxial opioids to control nausea and pruritus, there is the conceptual risk of depression of ventilation. However, diphenhydramine counteracts to some extent the opioid-induced decreases in the slope of the ventilatory response to CO₂ and does not exacerbate the opioid-induced depression of the hypoxic ventilatory response during moderate hypercarbia.

The rich distribution of histamine receptors in the myocardium and coronary vasculature predisposes the heart to cardioregulatory changes during massive histamine release that characterizes type 1 immune-mediated hypersensitivity (anaphylactic) reactions. Use of antihistamines in the acute treatment of anaphylactic reactions is directed at blocking further histamine-mediated respiratory sequelae and other systemic complications.

The administration of epinephrine is indicated as first-line therapy for the treatment of anaphylaxis. H₁ and H₂ antihistamines may be helpful in treating cutaneous and upper respiratory signs and symptoms of anaphylaxis and are considered second-line therapies, along with other drugs, including glucocorticoids.¹⁸

Concerns of possible attenuation of H₂-mediated increases in inotropy and chronotropy, thereby limiting potential cardioexcitatory compensatory mechanisms, does not seem to be clinically significant.

Histamine-receptor antagonists may also be administered prophylactically for anaphylactoid reactions to radiocontrast dyes. Second-generation H₁-receptor antagonists such as terfenadine, fexofenadine, and astemizole have low water solubility, and, unlike first-generation drugs, are not available for parenteral use.

Dimenhydrinate is an H₁-receptor antagonist that is the theoclate salt of diphenhydramine.

Dimenhydrinate has been used to treat motion sickness as well as postoperative nausea and vomiting. It is speculated that the efficacy of dimenhydrinate in motion sickness and inner ear diseases may be due to inhibition of the integrative functioning of the vestibular nuclei by decreasing vestibular and visual input. Manipulation of the extraocular muscles as in strabismus surgery may trigger an “oculoemetic” reflex similar to the well-described oculocardiac reflex. If the afferent arc of this reflex is also dependent on the integrity of the vestibular nuclei apparatus, then dimenhydrinate may attenuate or block this reflex and decrease the incidence of postoperative nausea and vomiting. Administration of dimenhydrinate, 20 mg intravenously (IV), to adults decreases vomiting after outpatient surgery. In children, dimenhydrinate, 0.5 mg/kg IV, significantly decreases the incidence of vomiting after strabismus surgery and is not associated with prolonged sedation. Compared with 5-HT antagonists, dimenhydrinate is an inexpensive antiemetic.

Side Effects

First-generation H₁ antagonists often have adverse effects on the CNS, including somnolence, diminished alertness, slowed reaction time, and impairment of cognitive function. Because there is some cross-reactivity with muscarinic receptors, anticholinergic effects such as dry mouth, blurred vision, urinary retention, and impotence may be seen. Tachycardia is common, and prolongation of the QTc interval on the electrocardiogram, heart block, and cardiac arrhythmias have occurred. First-generation H₁-receptor antagonists are still prescribed because they are effective and inexpensive. Administration of these drugs at bedtime is sometimes recommended because drug-related somnolence is of no concern during the night. Indeed, H₁-receptor antagonists may be sold as nonprescription sleeping aids.

Second-generation H₁ antagonists are unlikely to produce CNS side effects such as somnolence unless the recommended doses are exceeded. Enhancement of the effects of diazepam or alcohol is unlikely by second-generation drugs. Fexofenadine, a metabolite of terfenadine, does not prolong the QTc interval on the electrocardiogram, even in large doses. Patients with hepatic dysfunction, cardiac disorders associated with prolongation of the QTc interval, or metabolic disorders such as hypokalemia or hypomagnesemia may be especially prone to adverse cardiovascular effects of H₁-receptor antagonists. Most second-generation H₁-receptor antagonists are not removed by hemodialysis.

Antihistamine intoxication is similar to anticholinergic poisoning and may be associated with seizures and cardiac conduction abnormalities resembling tricyclic antidepressant overdose. Older nonsedating antihistamine drugs (terfenadine, astemizole) were associated with prolongation of the QTc interval and atypical (*torsades de pointes*) ventricular tachycardia, both after overdose and after coadministration with macrolide antibiotics or other drugs that interfere with their elimination. These drugs were removed from the market in 1999.

H₂-Receptor Antagonists

Cimetidine, ranitidine, famotidine, and nizatidine are H₂-receptor antagonists that produce selective and reversible inhibition of H₂ receptor-mediated secretion of hydrogen ions by parietal cells in the stomach ([Figures 35.2](#) and [35.3](#)). The relationship between gastric hypersecretion of fluid containing high concentrations of hydrogen ions and peptic ulcer disease emphasizes the potential value of a drug that selectively blocks this response. Despite the presence of H₂ receptors throughout the body, inhibition of histamine binding to the receptors on gastric parietal cells is the major beneficial effect of H₂-receptor antagonists.

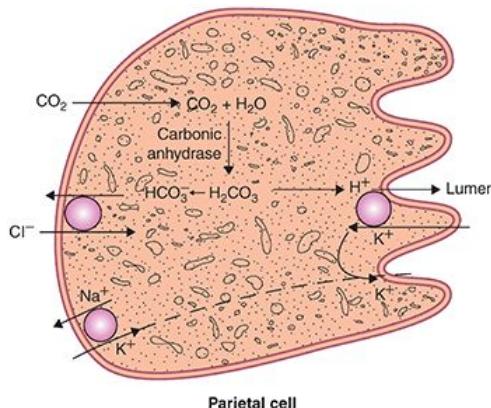


FIGURE 35.2 Ion flux through parietal cell.

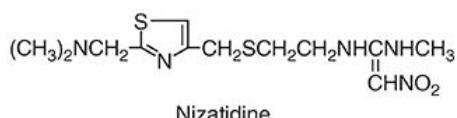
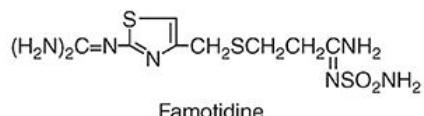
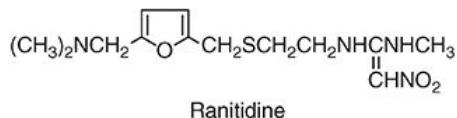
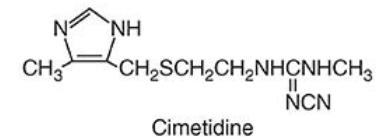


FIGURE 35.3 H₂-receptor antagonists.

Mechanism of Action

The histamine receptors on the basolateral membranes of acid-secreting gastric parietal cells are of the H₂ type and thus are not blocked by conventional H₁ antagonists. The occupation of H₂ receptors by histamine released from mast cells and possibly other cells activates adenylate cyclase, increasing the intracellular concentrations of cyclic adenosine monophosphate (cAMP). The increased concentrations of cAMP activates the proton pump of gastric parietal cells (an enzyme designated as hydrogen-potassium-ATPase) to secrete hydrogen ions against a large concentration gradient in exchange for potassium ions. H₂-receptor antagonists competitively and selectively inhibit the binding of histamine to H₂ receptors, thereby decreasing the intracellular concentrations of cAMP and the subsequent secretion of hydrogen ions by the parietal cells.

The relative potencies of the four H₂-receptor antagonists for inhibition of secretion of gastric hydrogen ions varies from 20- to 50-fold, with cimetidine as the least potent and famotidine the most potent ([Table 35.2](#)). The duration of inhibition ranges from approximately 6 hours for cimetidine to 10 hours for ranitidine, famotidine, and nizatidine. None of the four H₂-receptor antagonists has produced any consistent effects on

lower esophageal sphincter function or the rate of gastric emptying. Discontinuation of chronic H₂-receptor antagonist therapy is followed by rebound hypersecretion of gastric acid.

TABLE 35.2

Pharmacokinetics of H₂-receptor antagonists^a

	Cimetidine	Ranitidine	Famotidine	Nizatidine
Potency	1	4-10	20-50	4-10
EC ₅₀ (μ g/mL) ^b	250-500	60-165	10-13	154-180
Bioavailability (%)	60	50	43	98
Time to peak plasma concentration (hours)	1-2	1-3	1.0-3.5	1-3
Volume of distribution (L/kg)	0.8-1.2	1.2-1.9	1.1-1.4	1.2-1.6
Plasma protein binding (%)	13-26	15	16	26-35
Cerebrospinal fluid: plasma	0.18	0.06-0.17	0.05-0.09	Unknown
Clearance (mL/minute)	450-650	568-709	417-483	667-850
Hepatic clearance (%)				
Oral	60	73	50-80	22
Intravenous	25-40	30	25-30	25
Renal clearance (%)				
Oral	40	27	25-30	57-65
Intravenous	50-80	50	65-80	75
Elimination half-life (hours)	1.5-2.3	1.6-2.4	2.5-4	1.1-1.6
Decrease dose in presence of renal dysfunction	Yes	Yes	Yes	Yes
Hepatic dysfunction	No	No	No	No
Interfere with drug metabolism by cytochrome P450 enzymes	Yes	Minimal	No	No

^aData from Feldman M, Burton ME. Histamine₂-receptor antagonists. Standard therapy for acid-peptic diseases. 1. *N Engl J Med.* 1990;323:1672-1680.

^bEC₅₀ denotes the plasma concentration of the drug necessary to inhibit the pentagastrin-stimulated secretion of hydrogen ions by 50%.

Pharmacokinetics

The absorption of cimetidine, ranitidine, and famotidine is rapid after oral administration. Because of extensive first-pass hepatic metabolism, however, the bioavailability of these drugs is approximately 50% (see [Table 35.2](#)). Nizatidine does not undergo significant hepatic first-pass metabolism, and its bioavailability after oral administration approaches 100%. The average time to peak plasma concentrations of the four H₂-receptor antagonists ranges from 1 to 3 hours after oral administration. Because the volume of distribution for all four drugs exceeds the body's total body water content, some binding (13%-35%) to proteins must occur (see [Table 35.2](#)).

Cimetidine is widely distributed in most organs but not fat. Approximately 70% of the total body content of cimetidine is found in skeletal muscles. The volume of distribution is not altered by renal disease but is increased by severe hepatic disease and can be altered by changes in systemic blood pressure and cardiac output. All four drugs are present in breast milk and can cross the placenta and blood-brain barrier. The presence of cimetidine in cerebrospinal fluid is increased in patients with severe hepatic disease. The dose of cimetidine may need to be decreased to avoid mental confusion in patients with severe liver disease. The volume of distribution of cimetidine is also decreased about 40% in elderly patients, presumably reflecting the decrease in skeletal muscle mass associated with aging.

Although there is considerable variation in the clearance and elimination half-lives of H₂-receptor antagonists, their plasma elimination half-lives range from 1.1 to 4 hours (see [Table 35.2](#)).²¹ The elimination of all four drugs occurs by a combination of hepatic metabolism, glomerular filtration, and renal tubular secretion. Hepatic metabolism is the principal mechanism for clearance from the plasma of oral doses of cimetidine, ranitidine, and famotidine, and renal excretion is the principal pathway for clearance from the plasma of an oral dose of nizatidine. The liver may metabolize 25% to 40% of an IV dose of nizatidine. Only nizatidine appears to have an active metabolite (*N*₂-monodesmethyl-nizatidine), possessing about 60% of the activity of the parent drug. Hepatic metabolism of cimetidine occurs primarily by conversion of its side chain to a thioether or sulfoxide, and these inactive products appear in the urine as 5-hydroxymethyl and/or sulfoxide metabolites. The renal clearance of all four H₂-receptor antagonists is typically 2 to 3 times greater than creatinine clearance, reflecting extensive renal tubular secretion. Renal failure increases the elimination half-life of all four drugs, with the greatest effect on nizatidine and famotidine. Decreases in the doses of all four drugs are recommended for patients with renal dysfunction. Doses of H₂-receptor antagonists may also need to be decreased in patients with acute burns. Only 10% to 20% of total body cimetidine or ranitidine is cleared by hemodialysis.

Hepatic dysfunction does not seem to significantly alter the pharmacokinetics of H₂-receptor antagonists. Increasing age must be considered when determining the dose of H₂-receptor antagonists. For example, cimetidine clearance decreases 75% in patients between the ages of 20 and 70 years. There is also a 40% decrease in the volume of distribution of cimetidine in older patients. The elimination half-life of ranitidine and famotidine may be increased up to twofold in older patients.

Clinical Uses

H₂-receptor antagonists are most commonly administered for the treatment of duodenal ulcer disease associated with hypersecretion of gastric hydrogen ions. In the preoperative period, H₂-receptor antagonists have been administered as chemoprophylaxis to increase the pH of gastric fluid before induction of anesthesia. However, the ASA's practice guidelines for preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration state that there is evidence that H₂-receptor antagonists increase gastric pH and reduce gastric volume and may be administered preoperatively to patients at increased risk for aspirating. The routine preoperative use of medications that block gastric acid secretion to decrease the risks of pulmonary aspiration in patients who have no apparent increased risk for pulmonary aspiration is not recommended.⁵ When indicated though, H₂-receptor antagonists have been advocated as useful drugs in the preoperative period to decrease the risk of acid pneumonitis if inhalation of acidic gastric fluid were to occur in the perioperative period. One approach is to administer cimetidine, 300 mg orally (3-4 mg/kg), 1.5 to 2 hours before the induction of anesthesia, with or without a similar dose the preceding evening. Famotidine given the evening before and the morning of surgery or on the morning of surgery is equally effective in decreasing gastric fluid pH in outpatients and inpatients; there is no difference between famotidine doses of 20 and 40 mg.

Unfortunately, H₂-receptor antagonists, in contrast to antacids, have no influence on the pH of the gastric fluid that is already present in the stomach. Cimetidine crosses the placenta but does not adversely affect the fetus when administered before cesarean section. The other H₂-receptor antagonists have a profile similar to that of cimetidine with respect to placental transfer.

Preoperative preparation of patients with allergic histories or patients undergoing procedures associated with an increased likelihood of allergic reactions (radiographic contrast dye administration) may include prophylactic oral administration of an H₁-receptor antagonist (diphenhydramine, 0.5-1.0 mg/kg) and an H₂-receptor antagonist (cimetidine, 4 mg/kg) every 6 hours in the 12 to 24 hours preceding the possible triggering event. A corticosteroid administered at least 24 hours earlier is commonly added to this regimen.

The magnitude of the systemic blood pressure decrease that occurs in response to drug-induced (morphine, atracurium, mivacurium, and protamine) histamine release is decreased by prior administration of H₁- and H₂-receptor antagonists, confirming that prior occupation of histamine receptors with a specific

antagonist drug attenuates the cardiovascular effects of subsequently released histamine. Pretreatment with an H₁-receptor antagonist (diphenhydramine) or H₂-receptor antagonist (cimetidine) alone is not effective in preventing the cardiovascular effects of histamine that are released in response to drug administration, emphasizing the role of both H₁- and H₂-receptors in these responses. In fact, drug-induced histamine release may be exaggerated in patients pretreated with only H₂-receptor antagonists.

Side Effects

The frequency of severe side effects is low with all four H₂-receptor antagonists (**Table 35.3**). The risk for experiencing adverse side effects during treatment with an H₂-receptor antagonist is increased by the presence of multiple medical illnesses, hepatic or renal dysfunction, and advanced age. The most common adverse side effects are diarrhea, headache, fatigue, and skeletal muscle pain. Side effects that occur with a prevalence of <1% include mental confusion, dizziness, somnolence, gynecomastia, galactorrhea, thrombocytopenia, increased plasma levels of liver enzymes, drug fever, bradycardia, tachycardia, and cardiac arrhythmias. Cardiac reactions are most likely related to blockade of cardiac H₂ receptors. Mental confusion in patients being treated with cimetidine may be more likely in the presence of hepatic or renal dysfunction. Changes in mental status usually occur in the elderly and tend to be associated with high doses of cimetidine administered IV, often to patients in an intensive care unit. Most patients have an improvement in mental status 24 to 48 hours after discontinuing cimetidine. Ranitidine and famotidine also cross the blood–brain barrier and have been reported to produce mental confusion and to interfere with sleep.²² Mental confusion has rarely been observed in ambulatory patients being treated chronically with H₂-receptor antagonists.

TABLE 35.3

Side effects of H₂-receptor antagonists

Interaction with cerebral H ₂ receptors (headache, somnolence, confusion)
Interaction with cardiac H ₂ receptors (bradycardia, hypotension, heart block)
Hyperprolactinemia
Acute pancreatitis
Increased hepatic transaminase levels
Alcohol dehydrogenase dehydration
Thrombocytopenia
Agranulocytosis
Interstitial nephritis
Interference with drug metabolism by cytochrome P450

Cimetidine and, to a lesser extent, ranitidine increase the plasma concentrations of prolactin, which may result in galactorrhea in females and gynecomastia in males. Famotidine and nizatidine do not appear to increase plasma prolactin levels. Cimetidine, but not the other H₂-receptor antagonists, inhibits the binding of dihydrotestosterone to androgen receptors. Impotence and loss of libido may occur in males receiving chronic high-dose treatment with cimetidine.

The adverse effects of H₂-receptor antagonists on hepatic function are typically reflected by reversible increases in the plasma level of aminotransaminase enzymes, mostly in patients receiving large IV doses of H₂-receptor antagonists. H₂-receptor antagonists probably do not markedly alter hepatic blood flow.

Cardiac arrhythmia (sinus bradycardia, sinus arrest, sinus arrest with idioventricular escape rhythm, complete atrioventricular heart block) have been described after either oral or IV administration of H₂-receptor antagonists. Most of the described arrhythmias have occurred after chronic administration. Prolonged QTc interval and fatal cardiac arrest with famotidine have been reported. Cardiac effects of H₂-

receptor stimulation are similar to β_1 stimulation mediated by cAMP. This would explain why blockade of H_2 receptors might evoke bradycardia. Furthermore, blockade of H_2 receptors could increase H_1 -receptor effects, including negative dromotropy. Bradycardia and hypotension are generally associated with rapid IV administration of these drugs, most often to critically ill or older patients. The mechanism for hypotension appears to be peripheral vasodilation. A prudent approach is to administer these drugs over 15 to 30 minutes when administered IV.

Pulmonary infections from inhaled secretions may be more likely if the acid-killing effect on bacteria in the stomach is altered. Sustained increases of gastric fluid pH may lead to an overgrowth of other organisms such as *Candida albicans*. This may account for the occasional case of *Candida* peritonitis observed after peptic ulcer perforation in patients treated with an H_2 -receptor antagonist.

Drug Interactions

Numerous drug interactions have been described between H_2 -receptor antagonists and other drugs ([Table 35.4](#)). Drug interactions generally occur when a new drug is either started or discontinued. In this regard, measurement of plasma drug concentrations or laboratory measurements of an effect (prothrombin time) may be useful.

TABLE 35.4

Drug interactions with cimetidine^a

Drug	Effect of cimetidine on plasma concentration	Clearance of drug (% decrease)	Mechanism
Ketoconazole	Decreased	No change	Decreased absorption due to increased gastric fluid pH that slows dissolution
Warfarin ^b	Increased	23-36	Decreased hydroxylation of dextrorotatory isomer
Theophylline ^b	Increased	12-34	Decreased methylation
Phenytoin ^b	Increased	21-24	Decreased hydroxylation (?)
Propranolol	Increased	20-27	Decreased hydroxylation
Nifedipine	Increased	38	Unknown
Lidocaine	Increased	14-30	Decreased N-dealkylation
Quinidine	Increased	25-37	Decreased 3-hydroxylation (?)
Imipramine	Increased	40	Decreased N-demethylation
Desipramine	Increased	36	Decreased hydroxylation in rapid metabolizers
Triazolam	Increased	27	Decreased hydroxylation
Meperidine	Increased	22	Decreased oxidation
Procainamide ^b	Increased	28	Competition for renal tubular secretion

^aData from Feldman M, Burton ME. Histamine₂-receptor antagonists. Standard therapy for acid-peptic diseases. 1. *N Engl J Med*. 1990;323:1672-1680.

^bLesser drug interactions also occur with ranitidine.

The principal type of drug interaction reported with cimetidine is impairment of the hepatic metabolism of another drug because of the binding of cimetidine to the heme portion of the cytochrome P450 oxidase system. Cimetidine retards metabolism of drugs such as propranolol and diazepam that normally undergo high hepatic extraction. Slowed metabolism and prolonged elimination half-life with associated exaggerated pharmacologic effects of propranolol and diazepam have been documented with only 24 hours of treatment with cimetidine ([Figures 35.4](#) and [35.5](#)). In contrast, benzodiazepines, such as oxazepam and lorazepam, that are eliminated almost entirely by glucuronidation are not altered by cimetidine-induced effects on P450

enzyme activity. Cimetidine may slow metabolism of lidocaine and thus increase the possibility of systemic toxicity. In contrast, plasma concentrations of bupivacaine after epidural anesthesia for cesarean section are not influenced by a single dose of cimetidine administered before induction of anesthesia ([Figure 35.6](#)).

Ranitidine, although more potent than cimetidine, binds less avidly to the cytochrome P450 enzyme system and has less potential than cimetidine to alter the oxidative metabolism of other drugs. Famotidine and nizatidine do not bind notably to the cytochrome P450 enzyme system and thus have very limited potential for inhibiting the metabolism of other drugs.

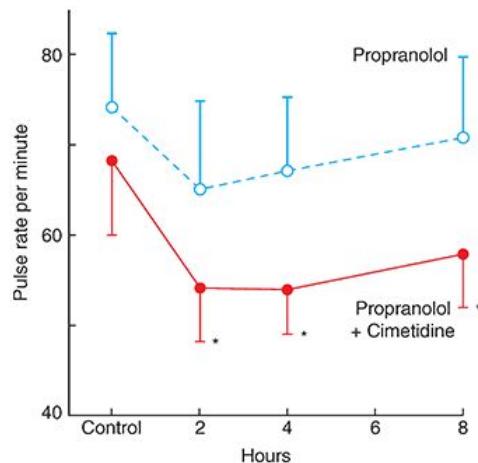


FIGURE 35.4 The effect of propranolol on resting heart rate is accentuated by the concomitant administration of cimetidine (mean \pm SD; $n = 5$; $*P < .05$). From Feely J, Wilkinson GR, Wood AJ. Reduction of liver blood flow and propranolol metabolism by cimetidine. N Engl J Med. 1981;304(12):692-695. Copyright © 1981 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

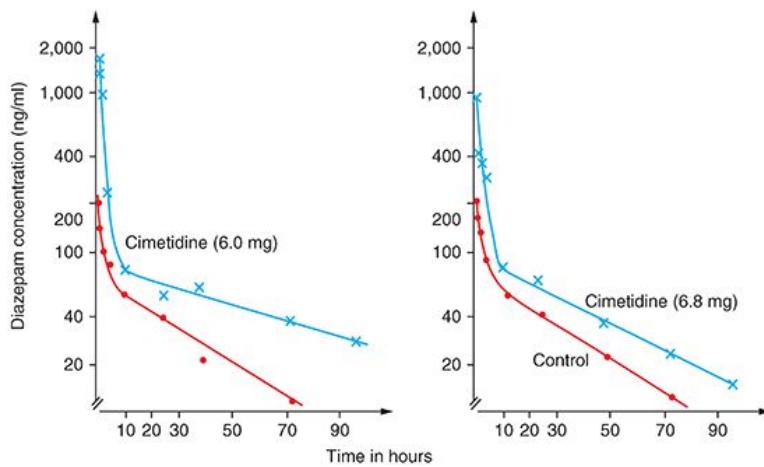


FIGURE 35.5 The rate of decline in the plasma concentration of diazepam, 0.1 mg/kg intravenous, is slowed by the prior administration of cimetidine, 6.0-6.8 mg/kg.

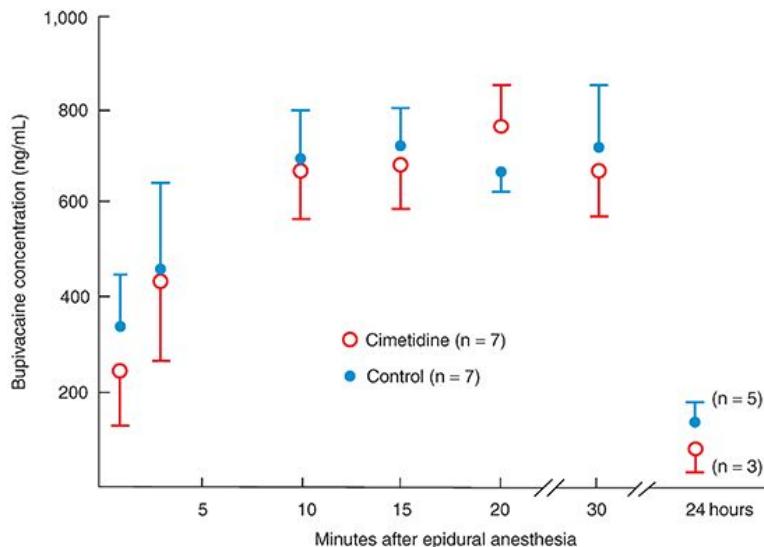


FIGURE 35.6 Maternal plasma levels of bupivacaine after administration of cimetidine ($n = 16$) 4 h or sodium citrate ($n = 20$) 10 min before cesarean section after epidural anesthesia. Reprinted with permission from Kuhnert BR, Zuspan KJ, Kuhnert PM, et al. Lack of influence of cimetidine on bupivacaine levels during parturition. Anesth Analg. 1987;66(10):986-990. Copyright © 1987 International Anesthesia Research Society.

H_2 -receptor antagonists compete with cationic compounds for renal tubular secretion. Because of the competition of cimetidine and ranitidine with creatinine for renal tubular secretion, serum creatinine levels are increased about 15%. Cimetidine and ranitidine, but not famotidine, impair renal tubular secretion of procainamide and theophylline. Famotidine, however, has been reported to interfere with phosphate absorption, leading to the development of hypophosphatemia. Impairment of renal theophylline clearance with cimetidine is probably negligible compared with impairment of the hepatic metabolism of theophylline.

Similar to oral antacids, all four H_2 -receptor antagonists have the potential to alter the absorption of some drugs by increasing the gastric fluid pH. Cimetidine has been reported to enhance the absorption of ethanol from the stomach as a result of inhibition of gastric alcohol dehydrogenase.

In addition to drug interactions produced by H_2 -receptor antagonists, several drugs alter the disposition of the antagonists. Magnesium and aluminum hydroxide antacids decrease by 30% to 40%, respectively, the bioavailability of cimetidine, ranitidine, and famotidine. Despite this impaired absorption, therapeutic blood levels of the H_2 antagonist can still be achieved, and rigorous separation of dosage schedules during combined drug therapy is probably unnecessary.

Proton Pump Inhibitors

Proton pump inhibitors (PPIs) (omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole) are the most effective drugs available for controlling gastric acidity and volume (Table 35.5). The final step in gastric acid secretion is the membrane enzyme proton pump (hydrogen-potassium-ATPase) that moves hydrogen ions across the gastric parietal cell membranes in exchange for potassium ions. The secretion of HCl by gastric parietal cells ultimately depends on the function of the proton (hydrogen ion) pump. PPIs are more effective than H_2 -receptor antagonists for healing esophagitis and preventing relapse. PPIs also appear to be more effective than H_2 -receptor antagonists for relieving heartburn, the cardinal feature of “gastroesophageal reflux disease.” However, for patients without esophagitis and infrequent symptoms H_2 -receptor antagonists are more cost-effective.

Choice of PPI

The available PPIs are interchangeable when a decrease in gastric pH following a single dose is the goal.¹⁹ The PPIs, compared to H₂-receptor antagonists, have been associated with an almost one-third increase in the incidence of *C difficile* infection²³ and with an increased incidence of pneumonia in patients who have sustained a cerebrovascular accident,²⁴ presumably because of the loss of a bactericidal acidic environment in the stomach. For these and other reasons, there are those who believe that we should be more selective in patients to whom we administer PPIs.²⁵

TABLE 35.5

Pharmacokinetics of proton pump inhibitors

	Bioavailability	Time to peak plasma concentration (hour)	Protein binding	Elimination half-life (hour)	Hepatic metabolism	Interference with cytochrome P450
Omeprazole	60%	2-4	>90%	0.5-1.0	Yes	Minimal
Esomeprazole	60%	2-4	>90%	0.5-1.0	Yes	Minimal
Lansoprazole	85%	1.5-3.0	97%	1.5	Yes	Minimal
Pantoprazole	77%	2.5	98%	1.9	Yes	No
Rabeprazole	85%	2.9-3.8	96%	1	Yes	No

Omeprazole

Omeprazole is a substituted benzimidazole that acts as a prodrug that becomes a PPI (Figure 35.7). As a weak base, omeprazole is concentrated in the secretory canaliculi of the gastric parietal cells, where it is protonated to its active form. The initial dose of omeprazole will only inhibit those proton pumps present on the luminal surface. As pumps are generated and inserted into the luminal surfaces, additional doses are required to inhibit these new pumps. Therefore, omeprazole takes several days to exert its maximal inhibitory effect on gastric acid secretion. Daily administration results in about 66% inhibition of gastric acid secretion by about 5 days. Likewise, discontinuation of omeprazole is not followed immediately by return of gastric acid secretion.

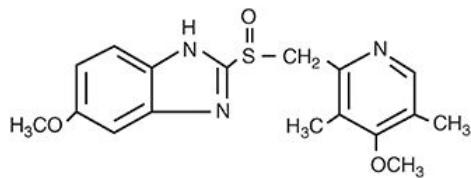


FIGURE 35.7 Omeprazole.

Omeprazole provides prolonged inhibition of gastric acid secretion, regardless of the stimulus, and it inhibits daytime and nocturnal acid secretion and meal-stimulated acid secretion to a significantly greater degree than do the H₂-receptor antagonists. This drug heals duodenal and possibly gastric ulcers more rapidly than do the H₂-receptor antagonists. In patients with bleeding peptic ulcers and signs of recent bleeding, treatment with omeprazole decreases the rate of bleeding and the need for surgery. Omeprazole is superior to H₂-receptor antagonists for the treatment of reflux esophagitis and is the best pharmacologic treatment of Zollinger-Ellison syndrome.

Preoperative Medication

As preoperative medication, omeprazole effectively increases gastric fluid pH and decreases gastric fluid volume in children and adults. In this regard, the onset of the gastric antisecretory effect of omeprazole after a single oral dose (20 mg) occurs within 2 to 6 hours. The duration of action is prolonged (>24 hours) because the drug is concentrated selectively in the acidic environment of gastric parietal cells. Omeprazole, 20 mg,

orally administered the night before surgery increases gastric fluid pH, whereas administration on the day of surgery (up to 3 hours before induction of anesthesia) fails to improve the environment of the gastric fluid. This suggests that oral omeprazole should be administered >3 hours before anticipated induction of anesthesia for chemoprophylaxis. If sufficient time is not available, the administration of bicarbonate with omeprazole has been demonstrated to achieve the desired decrease in gastric pH.²⁶

Side Effects

Omeprazole crosses the blood–brain barrier and may cause headache, agitation, and confusion. Gastrointestinal side effects include abdominal pain, flatulence, nausea, and vomiting. Small bowel bacterial overgrowth may occur owing to acid suppression.¹⁴ The loss of the inhibitory effect of gastric acid results in increased plasma concentrations of gastrin. There is no need to decrease the dose of PPIs in the presence of renal or hepatic dysfunction.²¹

Esomeprazole

Esomeprazole is the levorotatory isomer of omeprazole that is metabolized differently in the liver, resulting in greater plasma concentrations of the drug compared with the racemic drug, omeprazole. The pharmacodynamic properties of esomeprazole are similar to those of omeprazole.

Pantoprazole

Pantoprazole is the most potent and fast acting of the available PPIs and is frequently administered in an intensive care unit as prophylaxis against stress-related mucosal damage. A 2019 study published in *The New England Journal of Medicine* found no difference between intensive care unit patients considered at risk for upper gastrointestinal bleeding who were administered pantoprazole versus placebo in terms of 90-day mortality and clinically important events.²¹

Gastrointestinal Prokinetics

Motility-modulating drugs exert their therapeutic effects by increasing lower esophageal sphincter tone, enhancing peristaltic contractions, and accelerating the rate of gastric emptying.

Dopamine Blockers

Domperidone

Domperidone is a benzimidazole derivative that, like metoclopramide, acts as a specific dopamine antagonist that stimulates peristalsis in the gastrointestinal tract, speeds gastric emptying, and increases lower esophageal sphincter tone ([Figure 35.8](#)). Domperidone is only available on a compassionate-use basis in the US.

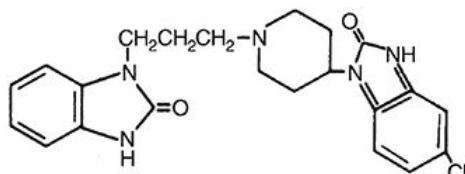


FIGURE 35.8 Domperidone.

Unlike metoclopramide, domperidone does not easily cross the blood–brain barrier and does not appear to have any anticholinergic activity. Its gastrokinetic actions have, therefore, been attributed to its peripheral dopaminergic activity. Because it lacks dopaminergic effects in the CNS, this drug is not associated with extrapyramidal symptoms. However, similar to metoclopramide, it does affect prolactin secretion by the pituitary. The FDA refused to give approval for domperidone's sale in the United States because of concerns about lactating women using domperidone to increase breast milk production because of the cardiac risks associated with its use (eg, cardiac arrhythmias, cardiac arrest, and sudden death). It is possible to obtain permission from the FDA to prescribe domperidone for nonlactating adults with gastrointestinal motility

disorders that are difficult to manage with available therapy, in whom domperidone's potential benefits outweigh its cardiac risks. Even in countries that allow its use, there is increasing concern because of the possibility of cardiac arrhythmias and sudden death²⁸ now thought to be secondary to inhibition of human Ether-a-go-go related gene (hERG) channel activity, which in turn decreases the rapid component of the cardiac delayed rectifier K⁺ current.²⁹

Metoclopramide

Metoclopramide acts as a gastrointestinal prokinetic drug that increases lower esophageal sphincter tone and stimulates motility of the upper gastrointestinal tract. It remains the only drug approved by the U.S. Food and Drug Administration (FDA) for the treatment of diabetic gastroparesis.²⁷ Gastric hydrogen ion secretion is not altered. The net effect is accelerated gastric clearance of liquids and solids (decreased gastric emptying time) and a shortened transit time through the small intestine.

Mechanism of Action

Metoclopramide produces selective cholinergic stimulation of the gastrointestinal tract (gastrokinetic effect) consisting of (1) increased smooth muscle tension in the lower esophageal sphincter and gastric fundus, (2) increased gastric and small intestinal motility, and (3) relaxation of the pylorus and duodenum during contraction of the stomach. The cholinergic stimulating effects of metoclopramide are largely restricted to smooth muscles of the proximal gastrointestinal tract and require some background cholinergic activity. There is evidence that metoclopramide sensitizes gastrointestinal smooth muscles to the effects of acetylcholine, which explains the observation that metoclopramide, unlike conventional cholinergic drugs, requires background cholinergic activity to be effective. Postsynaptic activity results from the ability of metoclopramide to cause the release of acetylcholine from cholinergic nerve endings. Indeed, atropine opposes metoclopramide-induced increases in lower esophageal sphincter tone and gastrointestinal hypermotility, indicating that metoclopramide acts on postganglionic cholinergic nerves intrinsic to the wall of the gastrointestinal tract.

Metoclopramide acts as a dopamine-receptor antagonist, but any effects on dopamine-induced inhibition of gastrointestinal motility are not considered to be clinically significant. However, metoclopramide does cross the blood–brain barrier, and within the CNS, metoclopramide inhibition of dopamine receptors can produce significant extrapyramidal side effects. In 2009, the FDA issued a boxed warning regarding the development of tardive dyskinesia with its use, and, since then, its use has decreased because the number of lawsuits has increased.³⁰ Metoclopramide's dopamine receptor antagonism also stimulates prolactin secretion, but its risk-benefit ratio is considered safer than that of a domperidone. Metoclopramide-induced antagonism of dopamine-agonist effects on the chemoreceptor trigger zone (located outside the blood–brain barrier) contributes to an antiemetic effect.

Pharmacokinetics

Metoclopramide is rapidly absorbed after oral administration, reaching peak plasma concentrations in 40 to 120 minutes. Extensive first-pass hepatic metabolism limits bioavailability to about 75%. Most patients achieve therapeutic plasma concentrations of 40 to 80 ng/mL after 10 mg of orally administered metoclopramide. The elimination half-life is 2 to 4 hours. Metoclopramide readily crosses the blood–brain barrier and the placenta. The concentration of metoclopramide in breast milk may exceed the plasma concentration. Approximately, 85% of an oral dose of metoclopramide appears in the urine, equally divided between unchanged drug and sulfate and glucuronide conjugates. Impairment of renal function prolongs the elimination half-life and necessitates a decrease in metoclopramide dosage.

Clinical Uses

Clinical uses of metoclopramide include (1) preoperative decrease of gastric fluid volume, (2) production of an antiemetic effect, (3) treatment of gastroparesis, (4) symptomatic treatment of gastroesophageal reflux, and (5) intolerance to enteral feedings in patients who are critically ill. Administration of metoclopramide, 10 to 20 mg IV, may be useful to speed gastric emptying before the induction of anesthesia, to facilitate small-

bowel intubation, or to speed gastric emptying to improve radiographic examination of the small intestine. Metoclopramide has been used to improve the effectiveness of oral medication if other drugs or the patient's underlying condition slows gastric emptying.

Preoperative Decrease in Gastric Fluid Volume

Metoclopramide, 10 to 20 mg IV over 3 to 5 minutes administered 15 to 30 minutes before induction of anesthesia, results in increased lower esophageal sphincter tone and decreased gastric fluid volume. More rapid IV administration may produce abdominal cramping. This gastric-emptying effect of metoclopramide may be of potential benefit before the induction of anesthesia in (1) patients who have recently ingested solid food; (2) trauma patients; (3) obese patients; (4) patients with diabetes mellitus and symptoms of gastroparesis; and (5) parturients, especially those with a history of esophagitis ("heartburn"), suggesting lower esophageal sphincter dysfunction and gastric hypomotility. Nevertheless, beneficial effects of metoclopramide on gastric fluid volume may be difficult to document in patients with low gastric fluid volumes who are awaiting elective surgery (**Table 35.6**).

TABLE 35.6

Volume of gastric contents and pH in study groups (mean \pm standard error)^a

	Metoclopramide (n = 30)	Placebo (n = 28)
Gastric volume (range)	24 \pm 2 mL (3-600)	30 \pm 5 mL (4-155)
Volume <25 mL	16 ^b (53%)	15 ^b (54%)
Gastric pH (range)	2.86 \pm 0.27 (1-6)	2.55 \pm 5 mL (1-5.5)
pH <2.5	12 ^b (40%)	16 ^b (57%)

^aData from Cohen SE, Jasson J, Talafre ML, Chauvelot-Moachon L, Barrier G. Does metoclopramide decrease the volume of gastric contents in patients undergoing cesarean section? *Anesthesiology*. 1984;61:604-607, with permission.

^bNumber of patients.

Regardless of the effects of gastric fluid volume, the administration of metoclopramide does not reliably alter gastric fluid pH. Furthermore, it is important to recognize that opioid-induced inhibition of gastric motility may not be reversible with metoclopramide. Likewise, the beneficial cholinergic stimulant effects of metoclopramide on the gastrointestinal tract may be offset by concomitant administration of atropine in the preoperative medication. Metoclopramide and other prophylactic drugs (antacids or H₂ antagonists) do not replace the need for proper airway management, including placement of a cuffed tracheal tube.

Production of an Antiemetic Effect

The antiemetic effect of metoclopramide in preventing postoperative nausea and vomiting has been debated. However, metoclopramide has been shown to decrease chemotherapy-induced nausea and vomiting and nausea and vomiting after cesarean section, although it is less efficacious than 5-HT₃ antagonists. The antiemetic property of metoclopramide probably results from antagonism of dopamine's effects in the chemoreceptor trigger zone. Additional antiemetic effects are provided by metoclopramide-induced increases in lower esophageal sphincter tone and facilitation of gastric emptying into the small intestine. These latter effects reverse the gastric immobility and cephalad peristalsis that accompany the vomiting reflex.

Side Effects

Metoclopramide should not be administered to patients with Parkinson disease or restless legs syndrome or who have movement disorders related to dopamine inhibition or depletion. In patients with no known movement disorders, dystonic extrapyramidal reactions (oculogyric crises, opisthotonus, trismus, torticollis, tardive dyskinesia) have been reported to occur in 1% to 10% of patients treated chronically with metoclopramide. However, a recent meta-analysis concluded that the incidence of tardive dyskinesia associated with metoclopramide is lower than this, ~0.1% per 1,000 patient-years. Patients at increased risk

are those who are older, female, diabetic, who have hepatic or renal failure, and those also taking antipsychotic drugs.³¹ Although extrapyramidal reactions may be a problem if large oral doses (40-80 mg daily) are administered chronically, there are reports of neurologic dysfunction related to the preoperative administration of a single dose of metoclopramide. These extrapyramidal reactions are identical to the parkinsonian syndrome evoked by antipsychotic drugs that antagonize the CNS actions of dopamine. Akathisia, a feeling of unease and restlessness in the lower extremities, may follow the IV administration of metoclopramide, resulting in cancellation of scheduled surgery, or may manifest in the postanesthesia care unit.

Abdominal cramping may follow rapid IV administration (<3 minutes) of metoclopramide. The IV administration of metoclopramide may also be associated with hypotension, tachycardia, bradycardia, and cardiac arrhythmia. Sedation, dysphoria, agitation, dry mouth, glossal or periorbital edema, hirsutism, and urticarial or maculopapular rash are rare side effects that have not been observed after single doses of metoclopramide. Breast enlargement, galactorrhea, or menstrual irregularities that occur rarely are presumed to reflect metoclopramide-induced increases in plasma prolactin concentrations. For this reason, patients with a history of breast cancer probably should not be treated chronically with metoclopramide.

Placental transfer of metoclopramide occurs rapidly, but adverse fetal effects with single doses have not yet been observed. The usual dopamine-induced inhibition of aldosterone secretion is prevented by metoclopramide. As a result, the possibility of sodium retention and hypokalemia should be considered, especially in patients who develop peripheral edema during chronic therapy.

Metoclopramide should probably not be administered in combination with phenothiazine or butyrophenone drugs or to patients with preexisting extrapyramidal symptoms or signs, as mentioned previously, or with seizure disorders. Patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants should likewise probably not receive metoclopramide. Metoclopramide decreases bioavailability of orally administered cimetidine by 25% to 50%. It would seem prudent not to administer metoclopramide to a patient with a suspected or known mechanical obstruction to gastric emptying. Likewise, metoclopramide is not administered after gastrointestinal surgery such as pyloroplasty or intestinal anastomosis because it stimulates gastric motility and may delay healing.

Metoclopramide has an inhibitory effect on plasma cholinesterase activity when tested in vivo, which may explain occasional observations of prolonged responses to succinylcholine and mivacurium in patients receiving these drugs and metoclopramide concomitantly. Parturients may be at increased risk for developing this response, considering the already decreased plasma cholinesterase activity associated with pregnancy. Likewise, the metabolism of ester local anesthetics could be slowed by metoclopramide-induced decreases in plasma cholinesterase activity.

Macrolides

The antibiotic erythromycin, as well as other macrolide antibiotics (ie, azithromycin), increases lower esophageal sphincter tone, enhances intraduodenal coordination, and promotes emptying of gastric liquids and solids in patients with diabetic gastroparesis, in patients awaiting emergency surgery, in patients without comorbidities, and in patients in the intensive care unit with food intolerance ([Figure 35.9](#)). The macrolide antibiotics' prokinetic properties are attributed to their binding to motilin receptors in the stomach and duodenum, although part of their prokinetic action may be secondary to cholinergic stimulatory properties. Side effects of the macrolide compounds are the same as for any antibiotic, and, therefore, because of concerns about tolerance, there are those that believe that erythromycin should only be used if all other prokinetic agents have failed.

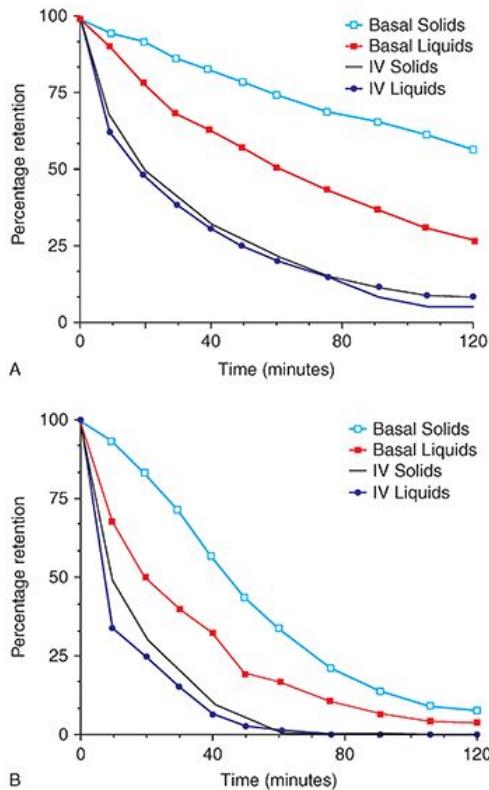


FIGURE 35.9 Erythromycin, 200 mg, administered intravenously over 15 minutes, followed by ingestion of a radioactive-labeled meal (scrambled egg, toast, and water) resulted in more rapid emptying of solids and liquids (intravenous [IV] solids and IV liquids) in patients with diabetic gastroparesis (A) and patients without diabetes (B) compared with gastric emptying times in the absence of erythromycin (basal solids and basal liquids). This research was originally published in *JNM*. Urbain JL, Vantrappen G, Janssens J, Van Cutsem E, Peeters T, De Roo M. Intravenous erythromycin dramatically accelerates gastric emptying in gastroparesis diabeticorum and normals and abolishes the emptying discrimination between solids and liquids. *J Nucl Med*. 1990;31(9):1490-1493. © SNMMI.

5-HT₄-Receptor Agonists

Nonselective 5-HT₄-receptor agonists, such as cisapride and mosapride, decrease acid reflux, increase lower esophageal sphincter tone, improve gastric motility, and increase motility in the small and large intestine by enhancing the release of acetylcholine from nerve endings in the myenteric plexus of the gastrointestinal mucosa. Opioid-induced gastric stasis, which is an important cause of postoperative nausea and vomiting, is reversed by cisapride. Tegaserod, a partial 5-HT₄-receptor agonist, improves small and large intestine transit and reduces constipation. Due to its relative nonselectivity, and because of side effects, cisapride was removed from the market several years ago.

Serotonin Agonists

Serotonin is involved in gastrointestinal motility and secretion, but studies of nonselective drugs that enhance serotonin action have not shown benefit.²⁷

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Nutrition

Michael J. Murray

In 1974, Charles Butterworth, MD, Chairman of the Council on Foods and Nutrition of the American Medical Association, published an article “The skeleton in the hospital closet.”¹ He commented that despite the knowledge of the importance of nutrition in recovery from illness and injury, few physicians made an effort to improve the nutritional status of their patients. In fact, just the opposite was true in that many hospitalized patients became malnourished, and some even starved, while in hospitals. More than four decades later, the same observation could be made, and, in fact, the points that Dr Butterworth made are probably as true now^{2,3} as they were then ([Table 36.1](#))

Despite the emphasis on improving outcomes by improving nutritional intake in hospitalized patients, few studies have shown a difference. A retrospective study of 1,223 patients concluded, “Early adequate feeding *may be* [emphasis added] associated with better outcomes.”⁴ Two prospective studies in 2017 and 2018, respectively, designed to ensure that patients received adequate nutrition support either by providing parenteral nutrition to supplement enteral feedings⁵ or by providing parenteral nutrition to patients able to take per os⁶ failed to demonstrate an improvement in mortality, infections, or length of stay (LOS). Because of the paucity of supporting literature, recent United States and European clinical practice guidelines on nutrition support in critically ill and injured patients are based more on expert opinion than on prospective, randomized, controlled studies.^{7,8}

One should not conclude that nutrition support is not beneficial. Rather than assuming that delivery of nutrients per se to patients will convert a catabolic state to an anabolic state, the underlying inflammatory state must be attenuated. Similarly, physical therapy modalities must be incorporated to “exercise” skeletal muscles;⁹ an immobile patient will inevitably lose muscle mass. No amount of nutrients will decrease the degree of frailty in a bedridden patient if an exercise regimen is not incorporated into the program.¹⁰

Likewise, one should not conclude that nutrition support, broadly defined, is not of importance to anesthesiologists. If anything, the increasing prevalence of enhanced recovery after surgery (ERAS) protocols, many of which incorporate nutritional regimens into the protocol,^{11,12} means that we should be familiar with the information that supports the efficacy of these protocols. During the preoperative phase of an ERAS protocol, patients should be screened for nutritional status.¹³ Those patients who are found to be malnourished (see in the following text) are advised to include nutritional supplements in their diet to promote anabolism. However, anabolism includes more than just nutrients; patients should be advised to embark on an exercise regimen that includes resistance training.⁹ On the day of surgery, prolonged fasting should be avoided, and preoperative oral carbohydrate fluids are recommended up until 2 hours before the surgical procedure.¹² The composition of the diet is probably less important than is the presence of fluid in the stomach, promoting peristalsis up until the time of surgery.¹⁴ There is evidence that simply chewing gum (along with the administration of alvimopan) prior to surgery is associated with a lower incidence of ileus and decreased hospital LOS.¹⁵ The administration of alvimopan, a peripherally acting μ -opioid receptor antagonist that inhibits the effects of opioids within the gastrointestinal tract, by itself is associated with a lower incidence of ileus, decreased LOS, and significant cost savings.¹⁶ This underscores the role of opioids in the development of ileus, especially in patients undergoing colorectal surgery.^{17,18} The American College of Surgeons Committee on Trauma has released a Trauma Quality Improvement Program Guideline on Acute Pain Management of patients who have sustained traumatic injury, emphasizing the role that multimodal pain management has in decreasing the use of opioids in the perioperative period. However, the guideline emphasizes that

opioids remain first-line therapy for moderate to severe pain.¹⁹ Patients whose severe pain is not controlled have a higher incidence of inadequate caloric input in the perioperative period.²⁰

TABLE 36.1

Practices that negatively impact the nutritional health of patients^a

- No one assumes primary responsibility for patient care
- Failure to optimize nutrition preoperatively
- No documentation of patient's food intake
- Patients kept nothing by mouth for diagnostic tests
- Little knowledge of the importance of certain nutrients in promoting health and recovery
- Lack of understanding of the increased nutritional needs due to traumatic injury or disease processes
- No comprehension of the role of nutrition in preventing infections
- Minimal communication between physicians and dietitians
- Institution of nutritional support only when the patient is in an advanced state of decline
- Not knowing which laboratory tests are helpful in evaluating adequacy of nutrition support

^aAdapted from Butterworth CE. The skeleton in the closet. *Nutr Today*. 1974;9:4-8.

Definitions

Malnutrition

The American Society of Parenteral and Enteral Nutrition and the Academy of Nutrition and Dietetics have defined *malnutrition* as reduced energy intake, unintentional weight loss, loss of subcutaneous fat, loss of muscle mass, fluid accumulation, and reduced grip strength. Its European counterpart, the European Society for Clinical Nutrition and Metabolism, combines weight loss with either age-related body mass index or fat-free mass index as a second alternative to low body mass index (less than 18.5 kg/m²).²¹ In the United States, the former definition is most widely used.

Enteral nutrition is defined as providing nourishment to a patient using a diet that is delivered directly into the gastrointestinal tract (nasogastric tube, nasointestinal tube, gastrostomy tube, jejunostomy tube).

Parenteral nutrition is defined as delivery of nutrients directly into the venous circulation (peripheral vein or central vein). The term *total parenteral nutrition* (TPN) is used when the only source of nutrient supply is via the parenteral route. Nutritional support is characterized as the use of enteral or parenteral nutrition rather than or in addition to an oral diet. Preexisting TPN should be continued during the perioperative period, whereas enteral nutrition should be discontinued about 6 hours before surgery (reflecting recommendations for food ingestion prior to elective surgery). However, relatively new guidelines promulgated in the United Kingdom for tracheally intubated patients recommend (1) enteral nutrition can be continued up until the patient is transferred to the operating theater for non-airway-related procedures and (2) prior to the procedure, itself, either the feeding tube or the oro- or nasogastric tube should be aspirated to empty the stomach. If manipulation of the airway is anticipated, for example, for a tracheostomy, the enteral feedings should be withheld for 6 hours prior to the procedure.¹¹

Nutrition Support

The TPN is intended to supply all the essential inorganic and organic nutritional elements necessary to maintain optimal body composition. Alimentation by the gastrointestinal tract, however (enteral nutrition), is preferred to intravenous (IV) alimentation (parenteral nutrition) because it is more physiologic. Enteral nutrition provides nutrients that stimulate trophic factors released from the lumen that maintains gut integrity and the absorptive activity of the small intestine. One observational study reported that greater protein and caloric intake in malnourished critically ill patients results in decreased mortality and LOS in the hospital.²² However, this was a retrospective study; in reality, the route of feeding is probably more important than is the amount of nutrition provided. There has been a great deal of interest recently in the microbiome (the community of microorganisms; eg, bacteria, fungi, viruses) of the gastrointestinal tract and how it can

influence the immune and nervous systems in both health and disease.²³ The benefits of periodic fasting to maintain weight and improve health may be related to changes within the microbiome of the gastrointestinal tract.²⁴ Even obesity has been shown to have adverse effects on the microbiome of the gut, known as dysbiosis, which affects immunity and insulin resistance.²⁵ Some of the medications we take such as statins are linked to a lower prevalence of gastrointestinal tract microbiome dysbiosis.²⁶ Of most importance in the present discussion are the effects of starvation on the microbiome, manifested by endocrine alterations, augmented inflammatory response, and decreased immune response, with adverse effects on the nervous system.²⁷ To the extent that enteral nutrition maintains the microbiome of the gastrointestinal tract, enteral nutrition should be used when possible, cognizant that, although enteral nutrition may decrease infectious complications and LOS, it has not yet been shown to decrease mortality.²⁸

Thus, even though benefit has not yet been demonstrated in terms of mortality, there are several other benefits. If the patient's caloric and nitrogen requirements cannot be met with luminal nutrition, enteral feedings should be used to partially meet needs, unless it is contraindicated (bowel obstruction, inadequate bowel surface area, intractable diarrhea). If enteral feeding is contraindicated and the patient is not malnourished or severely stressed, parenteral nutrition is not necessary for the first week following surgery or intensive care unit (ICU) admission because it has not been shown to be of benefit.^{29–31} The enteral and parenteral routes may be used simultaneously to meet nutritional requirements, although there is no evidence that the combination of the two to meet caloric needs improves outcomes.⁶ A 2019 Cochrane Review, "Enteral versus parenteral nutrition and enteral versus a combination of enteral and parenteral nutrition for adults in the intensive care unit," analyzed 25 studies that included more than 8,800 patients and found insufficient evidence to recommend whether enteral nutrition is better or worse than parenteral nutrition or better than a combination of the two. There was no difference in survivability at 90 or 180 days, no difference in adverse events, and no difference in ventilator for 3 days. Supporting the influence of enteral nutrition on the integrity of the gastrointestinal tract in decreasing the incidence of bacterial translocation, there was a lower incidence of sepsis in patients who received enteral over parenteral nutrition. Evidence that supported the concept that the amount of nutrients made a difference, was a lower mortality rate at 30 days when patients were given a combination of enteral and parenteral nutrition, but this effect did not extend to 90 or 180 days.²⁷

A recent large prospective study conducted in patients who were critically ill demonstrated that the administration of enteral glutamine supplemented with parenteral glutamine correlated with an increase in hospital mortality, 28-day mortality, and 6-month mortality.³² A subsequent meta-analysis of this and similar studies concluded, "Enteral glutamine supplementation does not confer significant clinical benefit in critically ill patients, with the exception of reduced hospital stay. There may be a significant benefit in patients with burns, but data are sparse, and larger randomized trials are warranted to confirm this effect."³³ Preoperative nutritional support should be reserved for malnourished patients undergoing major elective surgery; this recommendation is not commonly followed for a variety of reasons, but, if time permits, improvement in nutritional status is associated with an improvement in outcome.

Most patients do not need nutritional support, and clear-cut benefits of this expensive intervention have been established for only a select group of patients (**Table 36.2**). Patients not expected to resume adequate oral feedings within 7 to 10 days of surgery should begin nutritional support within 2 to 4 days postoperatively, within 1 to 2 days if they are in an ICU. Although the benefits of parenteral nutrition in the perioperative period are controversial, postoperative enteral feeding has been shown to decrease complication rates in malnourished patients, although mortality rates are unchanged.²⁸

TABLE 36.2

Established indications for use of nutritional support^a

- Major elective surgery in severely malnourished patients
- Major trauma (blunt or penetrating injury, head injury)
- Burns
- Hepatic dysfunction

- Renal dysfunction
- Bone marrow transplant recipients undergoing intensive chemotherapy
- Patients unable to eat or absorb nutrients for an indefinite period (neurologic impairment, pharyngeal dysfunction, or short bowel syndrome)
- Well-nourished, minimally stressed patients unable to eat for 7-10 days

^aAdapted from Souba WW. Nutritional support. *N Engl J Med.* 1997;336:41-48.

Severely injured patients, burn patients, and those with sepsis often are hypermetabolic, so directed nutritional support within 24 to 48 hours of admission may be beneficial. For example, energy requirements may double, and protein requirements may triple in severely burned patients.

Minimally stressed patients require about 25 to 30 cal/kg and 1 g/kg of protein daily to remain in nitrogen and energy equilibrium. Moderately to severely stressed patients should be resuscitated first and then started on a hypocaloric regimen (20 cal/kg) until the stress response abates. Lipid calories from infusions of propofol may be significant and should be included when calculating caloric intake.

Enteral Nutrition

Unless contraindicated (eg, short gut syndrome, circulatory shock), enteral nutrition is preferred over parenteral nutrition in almost every circumstance for the reasons mentioned earlier. Three decades ago, it was thought that the main goal of nutrition support in the hospitalized patient was to meet energy requirements so that an anabolic state would ensue. Current goals include meeting and attenuating the metabolic response to stress and, in addition, attenuating cellular injury and modulating the immune response to injury. Nutritional support of the moderately to severely injured patient includes enteral nutrition started sooner rather than later, pharmacotherapy (the provision of nutrients that modulate the body's response to injury), and glycemic control. Delivering early nutrition support, primarily using the enteral route, is seen as a proactive therapeutic strategy that *may* reduce disease severity, diminish complications, decrease LOS, and favorably impact patient outcome after severe injury. A variety of enteral solutions containing various amounts of protein (amino acids), carbohydrates (glucose), fat (medium- and long-chain triglycerides), micronutrients, macronutrients, and electrolytes are available. No single formulation has been found to be ideal for all patients. Carbohydrates can be the source of up to 90% of the calories, which increases the osmolarity of these solutions. Fat has a higher caloric density than do carbohydrates, and because it does not increase the osmolarity of the formula as much as carbohydrates, iso-osmolar solutions can be constituted. Unless the patient has malabsorption or maldigestion of fat (and even then a formula containing medium-chain triglycerides can be tried), formulas with a normal range of fat content (~30%) are preferred. Selection of a formula that provides sufficient total nitrogen as protein (1-1.5 g protein/kg per day) or amino acids is essential for all patients. It was once thought that low-protein formulations were indicated for patients with severe renal dysfunction; however, we now recognize that these patients require the same amount of protein as do other patients, even if one has to resort to some form of hemodialysis to maintain homeostasis. Specialized formulas are available for nutritional deficiencies associated with renal disease, but they are rarely indicated. The same can be said for patients with liver disease—standard enteral formulas work well. The only exception is the patient with hepatic encephalopathy for whom an enteral or parenteral formula containing branched-chain amino acids may improve the encephalopathy. Increased amounts of protein are indicated when the nitrogen requirement is increased, as in patients with trauma, burns, or sepsis. The efficient use of protein for anabolism depends on adequate caloric intake and implementation of an exercise program.

Enteral Tube Feeding

Enteral tube feeding may be necessary when patients are unable to orally consume nutritionally complete, liquefied food. Commercial formulations of natural foods can be so finely suspended that they pass through small-bore tubes. Defined-formula diets are necessary when luminal hydrolysis or absorption is impaired, as in malabsorption syndromes. An important consideration when using enteral nutrition is placement and positioning of the small-bore (8-12F) silastic delivery tube. Most often, patients receive continuous infusions

of enteral nutrition through a nasoenteric tube positioned in the stomach, duodenum, or jejunum. Several groups of investigators have studied whether there is a clinical significance between gastric and postpyloric feeding in various medical and surgical ICU settings. Two meta-analyses of these studies did not show a difference in the incidence of pneumonia whether the feeding tube was in the stomach or through the pylorus, nor was there a difference in mortality based on the position of the feeding tube.^{34,35} A more recent meta-analysis demonstrated similar findings,³⁶ as did a 2019 retrospective study of more than 100 patients.³⁷

Surgical placement of an esophagostomy or gastrostomy tube may be indicated for long-term feeding. For continuous enteral feeding, an automated infusion pump to control the rate of administration of the nutritional formula is useful. Absorption and tolerance are improved, and the incidence of side effects is decreased by continuous feedings. The rate of infusion is typically 60 to 90 mL per hour. This rate of infusion prevents the dumping syndrome, which may occur when hyperosmolar solutions are introduced rapidly into the small intestine.

Side Effects

Intolerance

There is a correlation between feeding intolerance and side effects, which include increased duration of time on a ventilator, greater LOS, and increased mortality.³⁸ Enteral feeding is frequently stopped when patients exhibit bloating or distention, emesis, distended abdomen on physical exam, absence of flatus, or abnormal findings on abdominal radiographs. Gastric residual volume (GRV) is frequently used as a surrogate for small intestinal intolerance in the absence of symptoms or physical findings, and in a recent survey of ICU nurses, 45% considered a GRV of less than 200 mL a reason to hold feedings.³⁹ However, nutrition specialists do not recommend interrupting enteral feedings for a GRV of less than 500 mL in the absence of other symptoms or signs of intolerance. A single measurement of an elevated GRV does not necessarily require cessation of enteral feedings, but a thorough exam should be conducted to ensure that the etiology of the intolerance would necessitate holding the feedings.⁴⁰

Because of the disparity of what is recommended based on expert opinion and what clinicians practice, there is a need for more objectivity as to when to stop enteral feedings.³⁸ Current guidelines call for the use of drugs that promote gastrointestinal motility (see [Chapter 35](#)) when GRV is increased and, if the response is inadequate, to decrease the rate of enteral feedings until the cause of the intolerance is identified and treated.^{7,8}

Diarrhea

The presence of diarrhea is always a concern, but one should consider alternative explanations before deciding that the diarrhea is caused by the osmolarity of the enteral product. Even if it is, osmotic diarrhea is usually relatively benign and short lasting. Osmotic diarrhea in this situation is a diagnosis of exclusion, and one must try to identify other causes, for example, *Clostridium difficile* infection.⁴¹ The Infectious Diseases Society of America and Society for Healthcare Epidemiology of America have recommended that, in institutions without guidelines on whom should be tested, a stool specimen should be tested for glutamate dehydrogenase antigen and toxin arbitrated by a nucleic acid amplification test. In institutions that have guidelines on whom should be tested for *C difficile* (unexplained, new onset, ≥ 3 unformed stools in 24 hours), a nucleic acid amplification test alone is sufficient.⁴² If these tests are not diagnostic, other causes of diarrhea should be considered, for example, enteral medications containing sorbitol or infections other than *C difficile*. The latter is diagnosed by sending stool for an assessment for fecal leukocytes, and, if positive, stool should be cultured. If clinically indicated, serum electrolyte levels should be measured to identify excessive loss or signs of dehydration.

Pulmonary aspiration is always a danger when enteral tube feeding is used. Patients should be maintained in a semisitting position (head of bed elevated 30 degrees), and, in patients at the highest risk for aspiration, the feeding tube should be placed through the pylorus. Preparations containing large amounts of electrolytes should be administered cautiously to patients with cardiovascular, renal, or hepatic disease. Many

commercial formulas contain large amounts of sodium. Dry preparations mixed with water are excellent culture media unless they are kept sterile and refrigerated.

PARENTERAL NUTRITION

Parentral nutrition is indicated for patients who are unable to ingest or digest nutrients or to absorb them from the gastrointestinal tract. Parenteral nutrition using isotonic solutions delivered through a peripheral vein is acceptable when the patient requires less than 2,000 calories daily and the anticipated need for nutritional support is brief. Peripheral veins do not tolerate infusion of solutions with an osmolarity that exceeds 750 mOsm/L (equivalent to 12.5% glucose), thus limiting the number of calories that can be administered. When nutritional requirements are greater than 2,000 calories daily or prolonged nutritional support is required, a catheter is placed in the central venous system to permit infusion of a hypertonic (1,900 mOsm/L) nutrition solution.

Short-Term Parenteral Therapy

Short-term parenteral therapy (3–5 days in patients without nutritional deficits) after uncomplicated surgical procedures is most often provided by hypocaloric, nonnitrogen, glucose-electrolyte solutions. For example, glucose solutions, 5% to 10%, with supplemental sodium, chloride, and other electrolytes, are commonly administered for short-term therapy. These solutions provide total fluid and electrolyte needs and sufficient calories to decrease protein catabolism and prevent ketosis. For example, daily infusion of approximately 150 g of glucose maintains brain and erythrocyte metabolism and decreases protein catabolism from skeletal muscles and viscera.

Amino acids may have a greater protein-sparing effect than does glucose, but amino acids without glucose do not completely prevent negative nitrogen balance after major surgery. The higher cost of amino-acid solutions relative to potential benefit has prevented their popularity for use in place of glucose for short-term therapy.

Peripheral infusion of fat emulsions may be administered as a nonprotein source of calories to augment those supplied by glucose.

Long-Term Total Parenteral Nutrition

The TPN (IV hyperalimentation) is the technique of providing total nutrition needs by infusion of amino acids combined with glucose and varying amounts of lipids. Lean body mass is preserved, wound healing may be enhanced, and there may even be improvement of an impaired immune-response mechanism.

The TPN solutions contain a large proportion of calories from glucose and thus are hypertonic. For this reason, these solutions must be infused into a central vein with a high blood flow to provide rapid dilution. A catheter is often placed percutaneously into the subclavian vein and guided into the right atrium. The parenteral nutrition solution is usually infused continuously over 24 hours. Because the solutions in current use are not nearly as hypertonic and hypercaloric as they once were, there is little concern about the patient becoming hypoglycemic if the infusion is discontinued abruptly but the potential for hypoglycemia should be considered.

Serum electrolytes, blood glucose concentrations, and blood urea nitrogen levels should be measured periodically during TPN. Tests of hepatic and renal function are also recommended but can be performed at less frequent intervals.

Side Effects

The side effects of TPN include infectious, mechanical, and metabolic complications. Among infectious complications, catheter-related sepsis is one of the most common and is associated with significant morbidity. The mechanical complications, such as pneumothorax and thrombosis if the catheter is left in place for extended periods, are complications related to the placement of a central line and with which anesthesiologists are familiar. A number of metabolic complications are seen more often with parenteral nutrition than with enteral nutrition ([Table 36.3](#)).

TABLE 36.3**Metabolic complications of parenteral nutrition**

Early complications	Late complications
Volume overload	Metabolic bone disease
Hyperglycemia	Hepatic steatosis
Hypophosphatemia (refeeding syndrome)	Hepatic cholestasis
Hypokalemia	Trace mineral deficiency
Hypomagnesemia	Vitamin deficiency
Hyperchloremic acidosis	

Sepsis

The TPN solutions infused through an IV catheter can support the growth of bacteria and fungi. A spiking temperature most likely reflects contamination via the delivery system or catheter. The catheter should be removed, and the tip cultured to determine the appropriate antibiotic therapy. In view of the hazard of contamination, the use of a central venous hyperalimentation catheter for administration of medications, as during the perioperative period, or for sampling of blood is not recommended.

Fatty Acid Deficiency

Fatty acid deficiency may develop during prolonged TPN but only if intralipid is not administered as part of a 3-in-1 formulation (protein, glucose, lipid). Possible immunosuppressive effects of lipid emulsions and an increased incidence of infections have led to recommendations to limit fat calories to about 30% of total TPN calories.

Hyperglycemia

Blood glucose concentrations should be monitored until glucose tolerance is demonstrated, which usually occurs after 2 to 3 days of therapy as endogenous insulin production increases. In addition, blood glucose concentrations should be periodically monitored during the perioperative period in patients maintained on TPN. The degree of hyperglycemia accompanying TPN is directly related to the rate of glucose infusion and to the degree of stress. A number of organizations have made recommendations on target glucose levels for patients undergoing an operation or in the ICU. The majority recommend a blood glucose target of 110 to 180 mg/dL,^{43,44} with some recommending lower levels of less than 150 mg/dL for cardiac surgical patients; however no benefit has been shown to more strict blood glucose control but with an increase in episodes of hypoglycemia.⁴⁵

Hypoglycemia

Accidental sudden discontinuation of the infusion of TPN solutions containing large amounts of glucose (catheter kink or disconnection) may cause hypoglycemia. The TPN infusions should be discontinued gradually over 60 to 90 minutes. Hypoglycemia occurs because the pancreatic insulin response does not always cease in parallel with discontinuation of the TPN solution. As a result, a high plasma concentration of insulin may persist in the absence of continued infusion of glucose. If administration of the TPN solution must be stopped abruptly, exogenous glucose should be infused for up to 90 minutes to prevent hypoglycemia. The incidence of hypoglycemia has decreased because clinicians have a lower daily caloric goal (eg, 1,400-2,000 kcal per day) compared with prior therapies (3,000-4,000 kcal per day).

Hepatobiliary Complications

Excessive caloric intake is associated with hepatic steatosis and steatohepatitis. An increased alkaline phosphatase or serum bilirubin concentrations warrant additional evaluation (eg, cholehepatic ultrasound).

Metabolic Acidosis

Hyperchloremic metabolic acidosis may occur because most of the amino acids in TPN are administered as their chloride salts.

Hypercarbia

In a patient with inadequate respiratory reserve, respiratory failure can develop when excessive carbohydrate calories are administered because of the increased carbon dioxide production. Because glucose has a respiratory quotient of 1, excessive glucose has been blamed on the respiratory failure associated with TPN, but we now know that excessive calories per se independent of their source increase carbon dioxide production and lead to respiratory failure in susceptible patients.

Monitoring During TPN

Acutely ill patients receiving TPN must be followed closely for the development of treatment-related complications. Access sites should be observed for signs of infection. Substitution of sodium or potassium acetate (metabolized to bicarbonate) for sodium or potassium chloride may be helpful should signs of hyperchloremic metabolic acidosis appear. Plasma triglyceride concentrations may increase in patients with diabetes mellitus, sepsis, and impaired hepatic or renal function. Vitamin K may need to be added to the TPN or administered intravenously based on measurement of prothrombin and plasma thromboplastin times. Monitoring of daily caloric intake, to ensure that caloric goals are being met, and fluid intake and output is needed as patients who are critically ill often experience significant fluid shifts.

Preparation of TPN Solutions

The TPN solutions are prepared from commercially available solutions by mixing hypertonic glucose with an amino acid solution. Sodium, potassium, phosphorus, calcium, magnesium, and chloride are added to the TPN solution. Trace elements, including zinc, copper, manganese, chromium, and selenium, must also be added if the need for parenteral therapy is prolonged. Requirements for vitamins may be increased, emphasizing the need to add a multivitamin preparation to TPN solutions. Vitamin B₁₂ and folic acid may be administered as components of a multivitamin preparation or separately. Vitamin D should be used sparingly because metabolic bone diseases may be associated with use of this vitamin in some patients on long-term TPN. Vitamin K can be administered separately once every week. The U.S. Food and Drug Administration (FDA) disallowed routine addition of vitamin K to TPN because of concern about side effects, and its routine administration would complicate the use of anticoagulants such as warfarin in patients who require such therapy. The serum albumin concentration will usually increase over several days to weeks as the stress response abates and if patients receive adequate nutrition support. The administration of supplemental albumin is not necessary in the absence of symptoms or signs of hypoalbuminemia, which usually do not occur until the serum albumin concentration is less than 2.4 g/dL.

Lipid emulsions can be administered separately or together with the glucose and amino acids to create a 3-in-1 TPN solution, as mentioned previously. To decrease the possibility of bacterial contamination, TPN solutions should be prepared aseptically under a laminar airflow hood, refrigerated, and administered within 24 to 48 hours.

Immunonutrition

Cellular immunity decreases during acute stress, as may accompany multiple organ system failure, sepsis, and shock. Immunonutrition is an attempt to enhance immunity and cellular integrity by incorporating specific additives (ω -3 fatty acids, arginine to enhance lymphocyte cytotoxicity, purines as a precursor of RNA and DNA, and antioxidants) into enteral diets. Currently, no well-controlled clinical studies have demonstrated improved outcomes with immunonutrition in patient populations that might benefit from their use, and there are no clinical guidelines that recommend their routine use in these patient populations.

Vitamins, Dietary Supplements, and Herbal Remedies

Vitamins

Vitamins are a group of structurally diverse organic substances (water soluble or fat soluble) that must be provided in small amounts in the diet for subsequent synthesis of cofactors that are essential for various metabolic reactions (**Table 36.4**). Food is the best source of vitamins, and healthy persons consuming an adequate balanced diet will not benefit from supplemental vitamins. Nevertheless, many persons do not consume adequate amounts of vitamin-rich foods, especially patients with alcoholism and malabsorption syndromes, older adults, and the economically disadvantaged.

TABLE 36.4

Vitamins

	Function	Deficiency	Toxic effects	Sources
Thiamine (B ₁)	Metabolism of carbohydrates, alcohol, amino acids	Beriberi Wernicke-Korsakoff syndrome	None	Grains Legumes Poultry Meat
Riboflavin (B ₂)	Cellular oxidation-reduction reactions	Stomatitis Dermatitis Anemia	None	Grains Dairy products Meat Eggs Green vegetables
Nicotinic acid (niacin; B ₃)	Oxidative metabolism Decreases LDL cholesterol Increases HDL cholesterol	Pellagra	Flushing Headaches Pruritus Hyperglycemia Hyperuricemia	Meat Poultry Fish Grains Peanuts Tryptophan in foods
Pyridoxine (B ₆)	Amino acid metabolism Heme synthesis Neuronal excitability Decreases blood homocysteine levels	Anemia Cheilosis Dermatitis	Neurotoxicity	Liver Poultry Fish Grains Bananas
Pantothenic acid	Metabolic processes	Rare	None	Many foods
B ₁₂ (cobalamin, cyanocobalamin)	DNA synthesis Myelin synthesis Decreases blood homocysteine levels	Megaloblastic anemia Peripheral neuropathies	None	Liver Poultry Fish Dairy products
Folic acid	DNA synthesis Decreases blood homocysteine levels	Megaloblastic anemia Birth defects	None	Legumes Grains Fruit Poultry Meat
Ascorbic acid (C)	Collagen synthesis Possible protection against certain cancers	Scurvy	Nephrolithiasis Diarrhea	Fruits Green vegetables Potatoes Cereals

A (retinol, retinoic acid)	Vision Epithelial integrity	Night blindness Susceptibility to infection	Teratogenicity Hepatotoxicity Cerebral edema	Liver Dairy products Green vegetables
D (calciferol)	Intestinal calcium absorption	Osteomalacia Rickets	Hypercalcemia	Dairy products Fish Eggs Liver
E (tocopherol)	Decreases peroxidation of fatty acids Possible protection against atherosclerosis	Rare	Antagonism of vitamin K Headaches	Vegetable oils Wheat germ Nuts
K	Synthesis of clotting factors (VII, IX, X)	Hemorrhagic diathesis	None	Green vegetables Intestinal bacteria

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Antioxidant vitamins can retard atherogenesis, and antioxidants may lower the risk of carcinogenesis. There is a demonstrated relationship between low dietary intake of antioxidants or low plasma concentrations of antioxidants and an increased risk of atherosclerosis and cancer. Studies have linked low plasma concentrations of folic acid, vitamin B₆, and vitamin B₁₂ with increased plasma concentrations of homocysteine and increased cardiovascular risks. A vitamin supplement that combines antioxidants with zinc can slow progression of macular degeneration. Individuals who consume multivitamins appear to have a decreased risk of cardiovascular disease and colon cancer, which may represent protection from folic acid and the B vitamins.

It is clear that additional information and studies are necessary to clarify the need for vitamin supplements in the presence of an adequate diet. The present recommendation is for parturients, older adults, and those individuals receiving a suboptimal nutritional diet to take a single multivitamin tablet daily. Strict vegetarians should take vitamin B₁₂ supplements.

Use of megadose vitamin preparations is not encouraged. Brand name and so-called all-natural preparations are no more effective than generic vitamin preparations. Regardless, vitamin supplements should never be used as a substitute for a balanced healthful diet that provides abundant quantities of vitamin-rich foods.

Water-Soluble Vitamins

Water-soluble vitamins include members of the vitamin B complex (thiamine, riboflavin, nicotinic acid, pyridoxine, pantothenic acid, biotin, cyanocobalamin, folic acid) and ascorbic acid (vitamin C) ([Figure 36.1](#)).

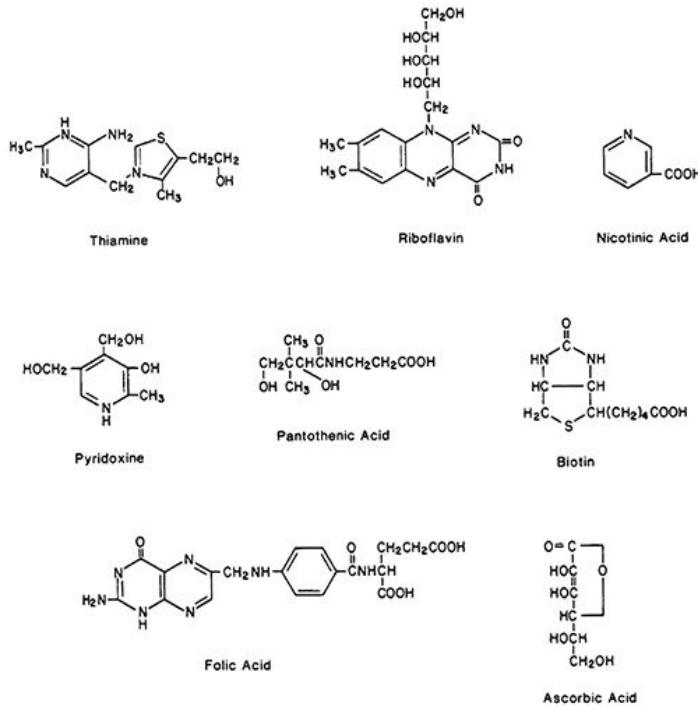


FIGURE 36.1 Chemical structure of water-soluble vitamins.

Thiamine

Thiamine (vitamin B₁) is converted to a physiologically active coenzyme known as *thiamine pyrophosphate*. This coenzyme is essential for the decarboxylation of α-keto acids such as pyruvate and in the use of pentose in the hexose-monophosphate shunt pathway. Increased plasma concentrations of pyruvate are a diagnostic sign of thiamine deficiency.

Causes of Deficiency

The requirement for thiamine is related to the metabolic rate and is greatest when carbohydrate is the source of energy. This is important in patients maintained by hyperalimentation in which the majority of calories are provided in the form of glucose. Such patients should receive supplemental amounts of thiamine. Thiamine requirements are also increased during pregnancy and lactation and in patients with chronic alcoholism.

Symptoms of Deficiency

Symptoms of mild thiamine deficiency (beriberi) include loss of appetite, skeletal muscle weakness, a tendency to develop peripheral edema, decreased systemic blood pressure, and low body temperature. Severe thiamine deficiency (Korsakoff syndrome), which may occur in alcoholics, is associated with peripheral polyneuritis, including areas of hyperesthesia and anesthesia of the legs, impairment of memory, and encephalopathy. High-output cardiac failure with extensive peripheral edema reflecting hypoproteinemia is often prominent. There is flattening or inversion of the T-wave prolongation of the QTc interval on the electrocardiogram.

Treatment of Deficiency

Severe thiamine deficiency is treated with IV administration of the vitamin. Once severe thiamine deficiency has been corrected, oral supplementation is acceptable.

Riboflavin

Riboflavin (vitamin B₂) is converted in the body to one of two physiologically active coenzymes: flavin mononucleotide or flavin adenine dinucleotide. Because of their ability to “accept” two hydrogen atoms, these coenzymes primarily influence hydrogen ion transport in oxidative enzyme systems, including cytochrome C reductase, succinic dehydrogenase, and xanthine oxidase.

Symptoms of Deficiency

Pharyngitis and angular stomatitis are typically the first signs of riboflavin deficiency. Later, glossitis, red denuded lips, seborrheic dermatitis of the face, and dermatitis over the trunk and extremities occur. Riboflavin deficiency is classically associated with angular cheilitis, photophobia, and scrotal dermatitis—the oral-ocular-genital syndrome. Anemia and peripheral neuropathy may be prominent. Corneal vascularization and cataract formation occur in some subjects. Treatment is with oral vitamin supplements that contain riboflavin.

Nicotinic Acid

Nicotinic acid (niacin; B₃) is converted to the physiologically active coenzyme nicotinamide adenine dinucleotide (NAD) and NAD phosphate; NAD is converted to NAD phosphate by phosphorylation. These coenzymes are necessary to catalyze oxidation-reduction reactions essential for tissue respiration.

Symptoms of Deficiency

Nicotinic acid is an essential dietary constituent, the lack of which leads to nausea, skin and mouth lesions, anemia, headaches, and tiredness. Chronic niacin deficiency is manifested by pellagra in which the skin characteristically becomes erythematous and rough in texture, especially in areas exposed to sun, friction, or pressure. The chief symptoms referable to the digestive tract are stomatitis, enteritis, and diarrhea. The tongue becomes very red and swollen. Salivary secretions are excessive, and nausea and vomiting are common. In addition to dementia, motor and sensory disturbances of the peripheral nerves also occur, mimicking changes that accompany a deficiency of thiamine.

The dietary requirement for niacin can be satisfied not only by nicotinic acid but also by nicotinamide and the amino acid tryptophan. The relationship between nicotinic acid requirements and the intake of tryptophan explains the association of pellagra with tryptophan-deficient corn diets. Carcinoid syndrome is associated with diversion of tryptophan from the synthesis of nicotinic acid to the production of serotonin (5-hydroxytryptamine), leading to symptoms of pellagra. Isoniazid inhibits incorporation of nicotinic acid into NAD and may produce pellagra.

Pellagra is uncommon in the United States, reflecting the supplementation of flour with nicotinic acid. Common causes of pellagra include chronic gastrointestinal disease and alcoholism, which are characteristically associated with multiple nutritional deficiencies. When pellagra is severe, IV administration of nicotinic acid is indicated. In less severe cases, oral administration of nicotinic acid is adequate. The response to nicotinic acid is dramatic, with symptoms waning within 24 hours after initiation of therapy.

Toxic effects of nicotinic acid include flushing, pruritus, hepatotoxicity, hyperuricemia, and activation of peptic ulcer disease. Nicotinic acid has also been prescribed to decrease the plasma concentrations of cholesterol and to increase the concentration of high-density lipoprotein.

Pyridoxine

Pyridoxine (vitamin B₆) is converted to its physiologically active form, pyridoxal phosphate, by the enzyme pyridoxal kinase. Pyridoxal phosphate serves an important role in metabolism as a coenzyme for the conversion of tryptophan to serotonin and methionine to cysteine.

Symptoms of Deficiency

Pyridoxine deficiency is uncommon and, when present, is associated with deficiencies of other vitamins and, if seen, is more likely to be seen in older adults, patients with alcoholism, and patients who are severely malnourished. Other patients who are at increased risk for manifesting deficiency are those with chronic renal failure on dialysis, those with hepatic failure, patients with rheumatoid arthritis, women with type 1 diabetes,

and those patients infected with human immunodeficiency virus. Certain drugs such as anticonvulsants and corticosteroids can interfere with pyridoxine metabolism, as can isoniazid, cycloserine, penicillamine, and hydrocortisone. Seizures accompanying deficiency of pyridoxine and peripheral neuritis such as carpal tunnel syndrome are common. The lowered seizure threshold may reflect decreased concentrations of the inhibitory neurotransmitter γ -aminobutyric acid, the synthesis of which requires a pyridoxal phosphate-requiring enzyme.

As described previously, a person with a deficiency of pyridoxine may also have a deficiency of the other B vitamins.

Drug Interactions

Isoniazid and hydralazine act as potent inhibitors of pyridoxal kinase, thus preventing synthesis of the active coenzyme form of the vitamin. Indeed, administration of pyridoxine decreases the incidence of neurologic side effects associated with the administration of these drugs. Pyridoxine enhances the peripheral decarboxylation of levodopa and decreases its effectiveness for the treatment of Parkinson disease. There is a decrease in the plasma concentration of pyridoxal phosphate in patients taking oral contraceptives.

Pantothenic Acid

Pantothenic acid is converted to its physiologically active form, coenzyme A, which serves as a cofactor for enzyme-catalyzed reactions involving transfer of two carbon (acetyl) groups. Such reactions are important in the oxidative metabolism of carbohydrates, gluconeogenesis, and the synthesis and degradation of fatty acids.

Pantothenic acid deficiency in humans is rare, reflecting the ubiquitous presence of this vitamin in ordinary foods as well as its production by intestinal bacteria. No clearly defined uses of pantothenic acid exist, although it is commonly included in multivitamin preparations and in hyperalimentation solutions.

Biotin

Biotin is an organic acid that functions as a coenzyme for enzyme-catalyzed carboxylation reactions and fatty acid synthesis. In adults, a deficiency of biotin manifests as glossitis, anorexia, dermatitis, and mental depression. Seborrheic dermatitis of infancy is most likely a form of biotin deficiency. For this reason, it is recommended that formulas contain supplemental biotin.

Cyanocobalamin

Cyanocobalamin (cobalamin, vitamin B₁₂) and vitamin B₁₂ are generic designations that are used interchangeably to describe several cobalt-containing compounds (cobalamins). Dietary vitamin B₁₂ in the presence of hydrogen ions in the stomach is released from proteins and subsequently binds to a glycoprotein intrinsic factor. This vitamin-intrinsic factor complex travels to the ileum, where it interacts with a specific receptor and is then transported across the intestinal endothelium. After absorption, vitamin B₁₂ binds to a β -globulin, transcobalamin II, for transport to tissues, especially the liver, which serves as its storage depot.

Causes of Deficiency

Although humans depend on exogenous sources of vitamin B₁₂, a deficient diet is rarely the cause of a deficiency state. Instead, gastric achlorhydria and decreased gastric secretion of intrinsic factor are more likely causes of vitamin B₁₂ deficiency in adults. Antibodies to intrinsic factor may interfere with attachment of the complex to gastrin receptors in the ileum. Bacterial overgrowth may also prevent an adequate amount of vitamin B₁₂ from reaching the ileum. Surgical resection or disease of the ileum predictably interferes with the absorption of vitamin B₁₂. Nitrous oxide irreversibly oxidizes the cobalt atom of vitamin B₁₂ such that the activity of two vitamin B₁₂-dependent enzymes, methionine synthetase and thymidylate synthetase, are decreased.

Diagnosis of Deficiency

The plasma concentration of vitamin B₁₂ (cobalamin) is less than 200 pg/mL when there is a deficiency state. Measurements of gastric acidity may provide indirect evidence of a defect in gastric parietal cell function, whereas the Schilling test (radioactivity in the urine measured after oral administration of labeled vitamin B₁₂) can be used to quantify ileal absorption of vitamin B₁₂. Observation of reticulocytosis after a therapeutic trial of vitamin B₁₂ confirms the diagnosis.

Symptoms of Deficiency

Deficiency of vitamin B₁₂ results in defective synthesis of DNA, especially in tissues with the greatest rate of cell turnover. In this regard, symptoms of vitamin B₁₂ deficiency manifest most often in the hematopoietic and nervous systems. Changes in the hematopoietic system are most apparent in erythrocytes, but when vitamin B₁₂ deficiency is severe, a pronounced cytopenia may occur. Clinically, the earliest sign of vitamin B₁₂ deficiency is megaloblastic (pernicious) anemia. Anemia may be so severe that cardiac failure occurs, especially in older adults with limited cardiac reserves.

Encephalopathy is a well-recognized complication of vitamin B₁₂ deficiency, manifesting as myelopathy, optic neuropathy, and peripheral neuropathy, either alone or in any combination. Neurologic complications do not parallel the presence of megaloblastic anemia. Damage to the myelin sheath is the most obvious symptom of nervous system dysfunction associated with vitamin B₁₂ deficiency. Demyelination and cell death occur in the spinal cord and cerebral cortex, manifesting as paresthesias of the hands and feet and diminution of sensation of vibration and proprioception with resultant unsteadiness of gait. Deep tendon reflexes are decreased, and, in advanced states, loss of memory and mental confusion occur. Indeed, vitamin B₁₂ deficiency should be considered in older adults with psychosis. Folic acid therapy corrects the hematopoietic, but not nervous system, effects produced by vitamin B₁₂ deficiency.

Treatment of Deficiency

Vitamin B₁₂ is available in a pure form for oral or parenteral use or in combination with other vitamins for oral administration. These preparations are of little value in the treatment of patients with deficiency of intrinsic factor or ileal disease. In the presence of clinically apparent vitamin B₁₂ deficiency, oral absorption is not reliable; the preparation of choice is cyanocobalamin administered intramuscularly. For example, in the patient with neurologic changes, leukopenia, or thrombocytopenia, treatment must be aggressive. Initial treatment is with intramuscular administration of vitamin B₁₂ and oral administration of folic acid. An increase in the hematocrit does not occur for 10 to 20 days. The plasma concentration of iron, however, usually declines within 48 hours because iron is now used in the formation of hemoglobin. Platelet counts can be expected to reach normal levels within days of initiating treatment; the granulocyte count requires a longer period to normalize. Memory and sense of well-being may improve within 24 hours after initiation of therapy. Neurologic signs and symptoms that have been present for prolonged periods, however, often regress slowly and may never return to completely normal function. Indeed, neurologic damage after pernicious anemia develops that is not reversed after 12 to 18 months of therapy is likely to be permanent. Once initiated, vitamin B₁₂ therapy must be continued indefinitely at monthly intervals. It is important to monitor plasma concentrations of vitamin B₁₂ and examine the peripheral blood cells every 3 to 6 months to confirm the adequacy of treatment.

Hydroxocobalamin has hematopoietic activity similar to that of vitamin B₁₂ but appears to offer no advantage despite its somewhat longer duration of action. Furthermore, some patients develop antibodies to the complex of hydroxocobalamin and transcobalamin II. Large doses of hydroxocobalamin have been approved for treatment of cyanide poisoning due to nitroprusside. Conceptually, cyanide reacts with the cobalt in cyanocobalamin, decreasing cyanide ion concentration.

Folic Acid

Folic acid is transported and stored as 5-methyltetrahydrofolate after absorption from the small intestine, principally the jejunum. Conversion to the metabolically active form, tetrahydrofolate, is dependent on the

activity of vitamin B₁₂. Tetrahydrofolate acts as an acceptor of 1-carbon units necessary for (1) conversion of homocysteine to methionine, (2) conversion of serine to glycine, (3) synthesis of DNA, and (4) synthesis of purines. Supplies of folic acid are maintained by ingestion of food and by enterohepatic circulation of the vitamin. Virtually, all foods contain folic acid, but protracted cooking can destroy up to 90% of the vitamin.

Causes of Deficiency

Folic acid deficiency is a common complication of diseases of the small intestine, such as sprue, that interfere with absorption of the vitamin and its enterohepatic recirculation. Patients with alcoholism have reduced intake of folic acid because of their decreased intake of food, and enterohepatic recirculation may be impaired by the toxic effect of alcohol on hepatocytes. Indeed, alcoholism is the most common cause of folic acid deficiency, with decreases in the plasma concentrations of folic acid manifesting within 24 to 48 hours of continuous alcohol ingestion. Drugs that inhibit dihydrofolate reductase (methotrexate, trimethoprim) or interfere with absorption and storage of folic acid in tissues (phenytoin) may cause folic acid deficiency.

Symptoms of Deficiency

Megaloblastic anemia is the most common manifestation of folic acid deficiency. This anemia cannot be distinguished from that caused by a deficiency of vitamin B₁₂. Folic acid deficiency, however, is confirmed by the presence of a folic acid concentration in the plasma of less than 4 ng/mL. Furthermore, the rapid onset of megaloblastic anemia produced by folic acid deficiency (1-4 weeks) reflects the limited in vivo stores of this vitamin and contrasts with the slower onset (2-3 years) of symptoms and signs of vitamin B₁₂ deficiency.

Treatment of Deficiency

Folic acid is available as an oral preparation alone or in combination with other vitamins and either an oral preparation or as a parenteral injection. The therapeutic uses of folic acid are limited to the prevention and treatment of deficiencies. For example, pregnancy increases folic acid requirements, and oral supplementation, usually in a multivitamin preparation, is indicated. In the presence of megaloblastic anemia because of folic acid deficiency, the administration of the vitamin is associated with a decrease in the plasma concentration of iron within 48 hours, reflecting new erythropoiesis. Likewise, the reticulocyte count begins to increase within 48 to 72 hours, and the hematocrit begins to increase during the second week of therapy.

Folate Therapy

Vitamin therapy to lower homocysteine levels has been recommended for the prevention of restenosis after coronary angioplasty. This is based on the belief that homocysteine is thrombogenic and is a risk factor for coronary artery disease. Folate supplementation is an effective treatment of homocystinemia. There have been three Cochrane reviews of the literature on the benefits of folate therapy in cardiovascular disease, the most recent in 2017.⁴⁶ No benefit was found to vitamins B₆, B₉, or B₁₂ in lowering the incidence of myocardial infarction or death from any cause, although there was a lower incidence of stroke. Some have argued that it is reasonable to recommend folic acid to patients at risk for coronary artery disease, especially if they have kidney disease.⁴⁷

Leucovorin

Leucovorin (citrovorum factor) is a metabolically active, reduced form of folic acid. After treatment with folic acid antagonists, such as methotrexate, patients may receive leucovorin (rescue therapy), which serves as a source of tetrahydrofolate that cannot be formed due to drug-induced inhibition of dihydrofolate reductase.

Ascorbic Acid (Vitamin C)

Ascorbic acid is a six-carbon compound structurally related to glucose. This vitamin acts as a coenzyme and is important in a number of biochemical reactions, mostly involving oxidation. For example, ascorbic acid is necessary for the synthesis of collagen, carnitine, and corticosteroids. Ascorbic acid is readily absorbed from the gastrointestinal tract, and many foods, such as orange juice and lemon juice, have a high content of

ascorbic acid. When gastrointestinal absorption is impaired, ascorbic acid can be administered intramuscularly or intravenously. Apart from its role in nutrition, ascorbic acid is commonly used as an antioxidant to protect the natural flavor and color of many foods.

Despite contrary claims, there is little evidence to support the efficacy of even large doses of ascorbic acid in treating viral respiratory tract infections. A risk of large doses of ascorbic acid is the formation of kidney stones resulting from the excessive secretion of oxalate. Excessive ascorbic acid doses can also enhance the absorption of iron and interfere with anticoagulant therapy.

One and a half grams of vitamin C, along with 100 mg of thiamine and 50 mg of hydrocortisone every 6 hours, are used by some to treat the vasoplegia occasionally seen in patients following cardiopulmonary bypass. There is as much evidence to support this practice as there is to recommend methylene blue or hydroxocobalamin or angiotensin II to treat vasoplegia; that is to say, not very much. Clinicians, though, will resort to these modalities as a last ditch effort to treat septic shock or cardiogenic shock in patients who are not responding to catecholamines or vasopressin.⁴⁸

Symptoms of Deficiency

A deficiency of ascorbic acid is known as scurvy. Humans, in contrast to many other mammals, are unable to synthesize ascorbic acid, emphasizing the need for dietary sources of the vitamin to prevent scurvy. Specifically, humans lack the hepatic enzyme necessary to produce ascorbic acid from gluconate. Manifestations of scurvy include gingivitis, rupture of the capillaries with formation of numerous petechiae, and failure of wounds to heal. An associated anemia may reflect a specific function of ascorbic acid on hemoglobin synthesis. Scurvy is evident when the plasma concentration of ascorbic acid is less than 0.15 mg/dL.

Scurvy is encountered among older adults, alcoholics, and drug addicts. Ascorbic acid requirements are increased during pregnancy, lactation, and stresses such as infection or after surgery. Infants receiving formula diets with inadequate concentrations of ascorbic acid can develop scurvy. Patients receiving TPN should receive supplemental ascorbic acid. Urinary loss of infused ascorbic acid is large, necessitating daily doses of 200 mg to maintain normal concentrations in plasma of 1 mg/dL. Increased urinary excretion of ascorbic acid is caused by salicylates, tetracyclines, and barbiturates.

Fat-Soluble Vitamins

The fat-soluble vitamins are vitamins A, D, E, and K ([Figure 36.2](#)). They are absorbed from the gastrointestinal tract by a complex process that parallels absorption of fat. Thus, any condition that causes malabsorption of fat, such as obstructive jaundice, may result in deficiency of one or all these vitamins. Fat-soluble vitamins are stored principally in the liver and excreted in the feces. Because these vitamins are metabolized very slowly, overdose may produce toxic effects.

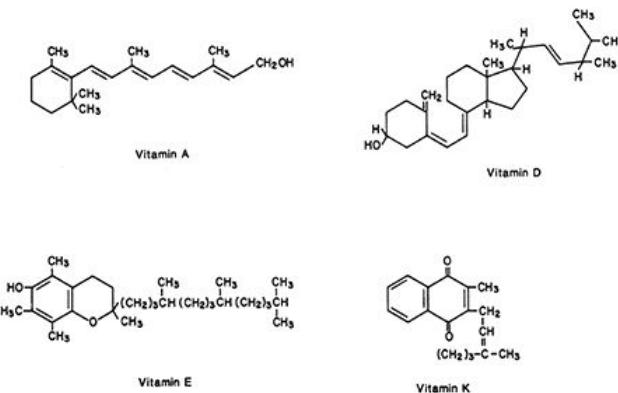


FIGURE 36.2 Chemical structure of fat-soluble vitamins.

Vitamin A (Retinol, Retinoic Acid)

Vitamin A exists in a variety of forms, including retinal and 3-dehydroretinal. This vitamin is important in the function of the retina, integrity of mucosal and epithelial surfaces, bone development and growth, reproduction, and embryonic development. It also has a stabilizing effect on various membranes and regulates membrane permeability. Vitamin A may exert transcriptional control of the production of specific proteins, a process that has important implications with respect to regulation of cellular differentiation and development of malignancies. Limitations in the therapeutic use of vitamin A for antineoplastic uses are the associated hepatotoxicity and its failure to distribute to specific organs.

Major dietary sources of vitamin A are liver, butter, cheese, milk, certain fish, and various yellow or green fruits and vegetables. Fish liver oils contain large amounts of vitamin A. Sufficient vitamin A is stored in the liver of well-nourished persons to satisfy requirements for several months. Plasma concentrations of vitamin A are maintained at the expense of hepatic reserves and thus do not always reflect a person's vitamin A status. Vitamin A may interact with cellular proteins, which function analogously to receptors for estrogens and other steroids.

Symptoms of Deficiency

Plasma concentrations of vitamin A of less than 20 µg/dL indicate the risk of deficiency. Most deficiencies occur in infants or children. Signs and symptoms of mild vitamin A deficiency are easily overlooked. Skin lesions such as follicular hyperkeratosis and infections are often the earliest signs of deficiency. Nevertheless, the most recognizable manifestation of vitamin A deficiency is night blindness (nyctalopia), which occurs only when the depletion is severe. Pulmonary infections are increased as mucous secretion from bronchial epithelium is decreased because the epithelial cells undergo keratinization. Keratinization and drying of the epidermis occurs. Urinary calculi are frequently associated with vitamin A deficiency, which may reflect epithelial changes that provide a nidus around which a calculus is formed. Abnormalities of reproduction include impairment of spermatogenesis and spontaneous abortion. Impairment of taste and smell is common in patients with vitamin A deficiency, presumably reflecting a keratinizing effect. Decreased erythropoiesis may be masked by abnormal losses of fluids.

Hypervitaminosis A

Hypervitaminosis A is the toxic syndrome that results from excessive ingestion of vitamin A, particularly in children. Typically, high vitamin A intake has resulted from overzealous prophylactic vitamin A therapy. Plasma concentrations of vitamin A of greater than 300 µg/dL are diagnostic of hypervitaminosis A. Treatment consists of withdrawal of the vitamin source, which is usually followed within 7 days by disappearance of the manifestations of excess vitamin A activity.

Early signs and symptoms of vitamin A intoxication include irritability, vomiting, and dermatitis. Fatigue, myalgia, loss of body hair, diplopia, nystagmus, gingivitis, stomatitis, and lymphadenopathy have been observed. Hepatosplenomegaly is accompanied by cirrhosis of the liver, portal vein hypertension, and ascites. Intracranial pressure may be increased, and neurologic symptoms, including papilledema, may mimic those of a brain tumor (pseudotumor cerebri). The diagnosis is confirmed by radiologic demonstration of hyperostoses underlying tender swellings on the extremities and the occipital region of the head. Plasma alkaline phosphatase concentrations are increased, reflecting osteoblastic activity. Hypercalcemia may occur because of bone destruction. Bones continue to grow in length but not in thickness, with increased susceptibility to fractures. Congenital abnormalities may occur in infants whose mothers have consumed excessive amounts of vitamin A during pregnancy. Psychiatric disturbances may mimic mental depression or schizophrenia.

Vitamin D

Vitamin D (calciferol) has two forms, D₂ (ergocalciferol) and D₃ (cholecalciferol), with identical chemical structure except that vitamin D₂ has an additional methyl group on carbon 24. Vitamin D₂ comes from the diet, whereas D₃ is synthesized in the skin by ultraviolet light's action on 7-dehydrocholesterol. Vitamin D₂ and D₃ are metabolically inert and require two chemical reactions to acquire activity. In hepatic cells, 25-hydroxylase adds a hydroxyl group to the molecule to form 25-hydroxyvitamin D or 25-(OH)D, and the

second reaction takes place in the kidney where 1α -hydroxylase converts 25-(OH)D to the biologically active 1,25(OH)₂ vitamin D (calcitriol), which regulates calcium and phosphate concentrations in the blood. A 25-(OH)D is transported in the blood by vitamin D-binding protein (DBP). Following its production in the kidney, calcitriol binds to DBP for transport to sites of action. A 25-(OH)D bound to DBP circulates in the blood, and when calcium levels decrease, 25-(OH)D is absorbed by the kidney and hydroxylated to the biologically active calcitriol and then released back into the bloodstream. The process is quite regulated, and, unless there is a need, calcitriol is not produced in the kidney. Traditionally, calcitriol has been thought to be the biologically active molecule and 25-(OH)D is a prohormone, but a study in knockout mice deficient in 1α -hydroxylase have demonstrated that sufficient calcium in diet can normalize serum calcium levels, presumably because of the action of 25-(OH)D.

Calcitriol exerts its effects by binding and activating vitamin D receptors (VDRs) in the nuclei of many different cell types. Calcitriol's primary function is to maintain calcium and phosphorous homeostasis. Calcium levels are maintained through three mechanisms: absorption of calcium in the duodenum and jejunum, release of calcium from bone, and increased uptake of calcium in the distal tubule of the kidney.

When phosphate levels are low, calcitriol increases its absorption in the small intestine, or, conversely, when phosphate levels are elevated, calcitriol acts on osteocytes to release fibroblast growth factor 23, which in turn increases the loss of phosphorous in the renal distal tubule.

The VDRs are identified in the nuclei of a wide variety of cells that do not play a role in calcium or phosphorus homeostasis, and it is not surprising then that vitamin D has a role in the regulation of many different genes.

Retrospective studies have shown a 21% reduction in mortality from cardiovascular disease and conversely a reduction by as much as 28% in mortality in those with vitamin D levels twice that of controls. However, supplementation with vitamin D to decrease the incidence of cardiovascular disease has not been shown, but there are advocates of such an approach to decrease the morbidity associated with cardiovascular disease.

Other studies have demonstrated a correlation between vitamin D concentrations and outcome in cancer patients. Calcitriol has a role in malignant disease, attenuating the proliferation of malignant cells through several mechanisms. Calcitriol may regulate the progression of malignant cell growth by suppressing the proto-oncogene myc, the cyclin-dependent kinases, and retinoblastoma protein phosphorylation and via interference of growth factor receptor-mediated signaling pathways. Calcitriol's impact on apoptosis may also have a role in its modulation of malignant cancerous cells.

Calcitriol may also influence immune function through similar metabolic pathways. In monocytes, calcitriol stimulates cathelicidin, a peptide with bactericidal and mycobactericidal properties. Calcitriol also inhibits the number and activity of T helper cells. These effects may be clinically important, with the former benefiting patients who are septic, and the latter, patients with myeloproliferative diseases.

Calcitriol might have a role in both type 1 and type 2 diabetes through its binding to the VDRs of pancreatic cells or through its effects on calcium metabolism. In addition to calcitriol's theoretical role in cardiovascular disease, cancer, immune function, and diabetes, it may also have an effect on morbidity and mortality patients who are critically ill.⁴⁹

Symptoms of Deficiency

A deficiency of vitamin D results in decreased plasma concentrations of calcium and phosphate ions, with the subsequent stimulation of parathyroid hormone secretion. Parathyroid hormone acts to restore plasma calcium concentrations at the expense of bone calcium. In infants and children, this results in failure to mineralize newly formed osteoid tissue and cartilage, causing formation of soft bone, which, with weight bearing, results in deformities known as rickets. In adults, vitamin D deficiency results in osteomalacia. Anticonvulsant therapy with phenytoin increases target organ resistance to vitamin D, resulting in an increased incidence of rickets and osteomalacia. There is evidence that vitamin D supplementation reduces the risk of falling among elderly individuals.

Hypervitaminosis D

Administration of excessive amounts of vitamin D results in hypervitaminosis, manifesting as hypercalcemia, skeletal muscle weakness, fatigue, headache, and vomiting. Early impairment of renal function from hypercalcemia manifests as polyuria, polydipsia, proteinuria, and decreased urine-concentrating ability. In addition to withdrawal of the vitamin, treatment includes increased fluid intake, diuresis, and administration of corticosteroids.

Vitamin E

Vitamin E (α -tocopherol) is not a single molecule but, rather, a group of fat-soluble substances occurring in plants. There is little persuasive evidence that vitamin E is nutritionally significant in humans. α -Tocopherol is the most abundant and important of the eight naturally occurring tocopherols that constitute vitamin E. An important chemical feature of the tocopherols is that they are antioxidants. In acting as an antioxidant, vitamin E presumably prevents oxidation of essential cellular constituents or prevents the formation of toxic oxidation products. There seems to be a relationship between vitamins A and E in which vitamin E facilitates the absorption, hepatic storage, and use of vitamin A. In addition, vitamin E seems to protect against the development of hypervitaminosis A by enhancing the use of the vitamin. Vitamin E is stored in adipose tissue and is thought to stabilize the lipid portions of cell membranes. Other functions attributed to vitamin E are inhibition of prostaglandin production and stimulation of an essential cofactor in corticosteroid metabolism.

Vitamin E requirements may be increased in individuals exposed to high oxygen environments or in those receiving therapeutic doses of iron or large doses of thyroid hormone replacement. Vitamin E may be important in hematopoiesis, with occasional forms of anemia responding favorably to the administration of α -tocopherol.

Despite absence of conclusive supportive evidence, vitamin E has been administered to women with a history of recurrent spontaneous abortions and for sterility in both sexes. In animals, vitamin E deficiency leads to the development of muscular dystrophy, but there is no evidence that a similar sequence occurs in humans. Changes similar to those observed in skeletal muscles have occurred in cardiac muscle of animals. A necrotizing myopathy with proximal skeletal muscle weakness and increased plasma concentrations of creatine kinase may occur in patients self-medicated with large doses of vitamin E. There are data that support an association between low plasma levels of vitamin E and the risk of developing lung cancer.

Epidemiologic studies have provided evidence of an inverse relationship between coronary artery disease and antioxidant intake and vitamin E supplementation in particular. This association has been attributed to finding that antioxidants prevent oxidation of lipids in low-density lipoproteins. It is proposed that oxidation of lipids in low-density lipoproteins (lipid peroxidation) initiates the process of atherogenesis.

Vitamin E is frequently recommended to prevent the development of age-related macular degeneration. The authors of a recent Cochrane review that included five randomized controlled trials involving more than 75,000 patients concluded that the consumption of vitamin E supplements does not influence the development of age-related macular degeneration. Because there is no benefit, and because of the risk of toxicity, the vitamin supplement for the prevention of age-related macular degeneration cannot be recommended.⁵⁰

Vitamin K

Vitamin K is a lipid-soluble dietary compound that is essential for the biosynthesis of several factors required for normal blood clotting. Phytonadione (vitamin K₁) is present in a variety of foods and is the only natural form of vitamin K available for therapeutic use. Vitamin K₂ represents a series of compounds that are synthesized by gram-positive bacteria in the gastrointestinal tract. Synthesis of vitamin K provides approximately 50% of the estimated daily requirement of vitamin K; the rest is supplied by the diet. Vitamin K is absorbed from the gastrointestinal tract only in the presence of adequate quantities of bile salts. Vitamin K accumulates in the liver, spleen, and lungs, but, despite its lipid solubility, significant amounts are not stored in the body for prolonged periods.

Mechanism of Action

Vitamin K functions as an essential cofactor for the hepatic microsomal enzyme that converts glutamic acid residues to γ -carboxyglutamic acid residues in factors II (prothrombin), VII, IX, and X. The γ -

carboxyglutamic acid residues make it possible for these coagulation factors to bind calcium ions and attach to phospholipid surfaces, leading to clot formation. If vitamin K deficiency occurs, the plasma concentrations of these coagulation factors decrease and a hemorrhagic disorder develops. Vitamin K deficiency is characterized by ecchymoses, epistaxis, hematuria, and gastrointestinal bleeding. Vitamin K activity is assessed by monitoring the prothrombin time.

Clinical Uses

Vitamin K is administered to treat its deficiency and attendant decrease in plasma concentrations of prothrombin and related clotting factors. Deficiency of vitamin K may be due to (1) inadequate dietary intake, (2) decreased bacterial synthesis due to antibiotic therapy, (3) impaired gastrointestinal absorption resulting from obstructive biliary tract disease and absence of bile salts, or (4) hepatocellular disease. Neonates have hypoprothrombinemia due to vitamin K deficiency until adequate dietary intake of the vitamin occurs and normal intestinal bacterial floras are established. Indeed, at birth, the normal infant has only 20% to 40% of the adult plasma concentrations of clotting factors II, VII, IX, and X. These plasma concentrations decrease even further during the first 2 to 3 days after birth and then begin to increase toward adult values after approximately 6 days. In premature infants, plasma concentrations of clotting factors are even lower. Human breast milk has low concentrations of vitamin K. Administration of vitamin K, 0.5 to 1.0 mg intramuscularly at birth, to the normal neonate prevents the decrease in concentration of vitamin K-dependent clotting factors in the first days after birth but does not increase these concentrations to adult levels.

Vitamin K replacement therapy is not effective when severe hepatocellular disease is responsible for the decreased production of clotting factors. In the absence of severe hepatocellular disease and the presence of adequate bile salts, the administration of oral vitamin K preparations is effective in reversing hypoprothrombinemia. Phytonadione and menadione are the vitamin K preparations most often used to treat hypoprothrombinemia.

Phytonadione

Phytonadione (vitamin K₁) is the preferred drug to treat hypoprothrombinemia, particularly if large doses or prolonged therapy is necessary. Hypoprothrombinemia of the neonate is treated with phytonadione, 0.5 to 1.0 mg intramuscularly, within 24 hours of birth.⁵¹ One indication for phytonadione is to reverse the effects of warfarin. Phytonadione, 10 to 20 mg orally or administered intravenously at a rate of 1 mg per minute, is usually adequate to reverse the effects of warfarin. The oral and intramuscular routes of administration are less likely than the IV injections of phytonadione to cause side effects and are thus preferred for nonemergency reversal of oral anticoagulants. Even large doses of phytonadione are ineffective against heparin-induced anticoagulation. Vitamin K supplementation is also indicated for patients receiving prolonged TPN, especially if antibiotics are concomitantly administered.

The IV injection of phytonadione may cause life-threatening allergic reactions characterized by hypotension and bronchospasm. Intramuscular administration may produce local hemorrhage at the injection site in hypoprothrombinemic patients. In neonates, doses of phytonadione of greater than 1 mg may cause hemolytic anemia and increase the plasma concentrations of unbound bilirubin, thus increasing the risk of kernicterus. The occurrence of hemolytic anemia reflects a deficiency of glycolytic enzymes in some neonates.

Menadione

Menadione has the same actions and uses as phytonadione ([Figure 36.3](#)). Water-soluble salts of menadione do not require the presence of bile salts for their systemic absorption after oral administration. This characteristic becomes important when malabsorption of vitamin K is due to biliary obstruction.

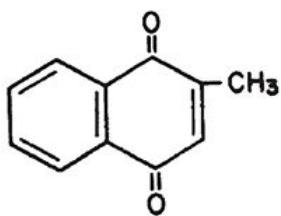


FIGURE 36.3 Chemical structure of menadione.

Menadione hemolyses erythrocytes in patients genetically deficient in glucose-6-phosphate dehydrogenase, as well as in neonates, particularly premature infants. This hemolysis and occasionally hepatic toxicity reflect a combination of menadione with sulphydryl groups in tissues. Kernicterus has occurred after menadione administration to neonates. For this reason, menadione is not recommended for treatment of hemorrhagic disease of the neonate. Administration of large doses of menadione or phytonadione may depress liver function, particularly in the presence of preexisting liver disease.

Dietary Supplements

Dietary supplements (vitamins, minerals, herbs, amino acids, enzymes) are products ingested orally and intended to supplement the diet with nutrients thought to improve health. Herbs include flowering plants, shrubs, seaweed, and algae. It is estimated that 25% of patients use alternative therapies characterized as dietary supplements or herbal remedies (more than 3 billion doses). These products are not subject to FDA approval because they are considered nutrients (do not undergo scientific testing to prove efficacy, and plants and parts of plants are not patent eligible), although they cannot be promoted specifically for treatment, prevention, or cure of disease. Nevertheless, these products can be labeled with statements describing their alleged effects. The FDA has no control over the herbal industry in terms of safety guidelines that would regulate purity and consistency of therapeutic medications.

Adverse Effects and Drug Interactions

Individuals who take dietary supplements and/or herbal remedies in combination with prescription drugs may be at risk for experiencing adverse interactions ([Tables 36.5](#) and [36.6](#)). The most serious side effects associated with these substances include cardiovascular instability, bleeding tendency (particularly in conjunction with other anticoagulants such as warfarin), and delayed awakening from anesthesia.

TABLE 36.5

Suggested uses, potential toxicities, and drug interactions of dietary supplements and herbal remedies

	Suggested uses	Potential toxicity	Drug interactions
Black cohosh	Menopausal symptoms	Gastrointestinal discomfort	Unknown
Chaste tree berries	Premenstrual symptoms	Pruritus	Dopamine-receptor antagonists
Cranberry	Urinary tract infections	Nephrolithiasis	Unknown
Dong quai	Menopausal symptoms	Rash	Warfarin
Echinacea	Upper respiratory infections	Hypersensitivity reactions Hepatic inflammation	
Evening primrose	Eczema Irritable bowel syndrome Premenstrual symptoms Rheumatoid arthritis	Nausea Vomiting Diarrhea Flatulence	Antiepileptic drugs
Feverfew	Prevent migraine	Hypersensitivity	Warfarin

	Arthritis Allergies	reactions Inhibits platelet activity	
Garlic	Hypertension Hypertriglyceridemia Hypercholesterolemia	Gastrointestinal discomfort Hemorrhage	Warfarin
Ginger	Motion sickness Vertigo	Unknown	Warfarin
Ginkgo biloba	Dementia Claudication Tinnitus	Gastrointestinal discomfort Headache Dizziness Bleeding Seizures	Warfarin
Ginseng	Fatigue Diabetes	Tachycardia Hypertension	Warfarin
Goldenseal	Laxative	Hypertension Edema	Unknown
Kava-kava	Anxiety	Rash Sedation Liver toxicity	Benzodiazepines Alcohol Anesthetic drugs
Kola nut	Fatigue	Irritability Insomnia	Stimulants
Licorice	Gastric ulcers	Hypertension	
Saw palmetto	Prostatic hyperplasia	Gastrointestinal discomfort	
St. John's wort	Depression Anxiety	Headache Insomnia Dizziness Gastrointestinal discomfort	Digoxin Oral contraceptives Serotonin antagonists Anesthetic drugs
Valerian	Insomnia	Headaches	Benzodiazepines Anesthetic drugs Antiepileptic drugs

TABLE 36.6

Suggested uses, potential toxicities, and drug interactions of nonherbal dietary supplements

	Suggested uses	Potential toxicity	Drug interactions
Coenzyme Q10	Congestive heart failure Hypertension	Dyspepsia Nausea Diarrhea	Warfarin
Glucosamine	Osteoarthritis	Gastrointestinal discomfort	Warfarin
Melatonin	Insomnia Jet lag	Fatigue Sedation	Unknown
S-adenosylmethionine	Osteoarthritis Depression	Nausea Gastrointestinal discomfort	Tricyclic antidepressants

Ephedra (*ma huang*) is a common ingredient in herbal weight loss products, stimulants, decongestants, and bronchodilators. The active moiety in ephedra is ephedrine, a sympathomimetic amine structurally related to amphetamines. Serious adverse reactions, including hypertension, cardiac arrhythmias, prolonged

QTc interval on the electrocardiogram, myocardial infarction, stroke, and death, have been described in patients taking ephedra. The chances of experiencing an adverse reaction when taking ephedra are estimated to be 100-fold greater than with any other dietary supplement or herbal remedy. Although tachycardia and vasoconstriction can occur in healthy patients, those with heart disease or systemic hypertension, or those who engage in strenuous physical exercise, seem to be at greatest risk for ephedra-related side effects. Based on the risk of adverse reactions, the FDA has concluded that dietary supplements containing ephedra present an unreasonable risk of illness or injury. The FDA banned sales of dietary supplements containing ephedra in April 2004.

Ginseng may cause tachycardia or systemic hypertension, particularly in combinations with other cardiac stimulant drugs. In addition, ginseng may decrease the anticoagulant effects of warfarin. Fever may enhance bleeding by inhibition of platelet activity. Warfarin may also be potentiated by concomitant use of garlic, ginkgo biloba, and ginger. Ginkgo biloba has been suggested to possess antiplatelet effects, and spontaneous hemorrhage has been reported. St. John's wort, which is alleged to be a natural antidepressant, has been shown to inhibit serotonin, dopamine, and norepinephrine reuptake and thus presents the possibility of interactions with monoamine oxidase inhibitors and other serotonergic drugs. Valerian, kava-kava, and possibly St. John's wort may delay awakening from anesthesia by prolonging sedative effects of anesthetic drugs.

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PART VII Endocrine System

Normal Endocrine Function

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Anesthesiologists face several preoperative challenges when patients with endocrine disorders need surgery. Patients may present with an endocrinopathy requiring surgery or more commonly have an endocrine abnormality, which complicates surgical and anesthetic management. Physiologic perturbations from the stress response of surgery may precipitate an endocrine crisis perioperatively.

Endocrine glands secrete hormones into the blood, which can act at distant sites (endocrine), adjacent to the site of origin (paracrine), at the site of origin (autocrine), and even within the site of origin (intracrine) to provoke a physiologic response. The endocrine system is evaluated by measuring hormone levels. In most cases, hormone output is regulated by a negative feedback system in which increased circulating plasma concentrations of the hormone decrease its subsequent release from the parent gland. The nervous system (via hypothalamic-releasing factors and peptides produced by the brain) and the immune system (via cortisol, cytokines, and interleukins) also modulate the endocrine system to regulate hormone levels. Defects in the pathway such as genetic receptor mutations or excessive circulating serum factors can cause endocrinologic dysfunction (hormone excess, hormone deficiency, and hormone resistance). Management of endocrinopathies includes hormone replacement and medical or surgical reduction of hormone levels produced by tumors.

Mechanism of Hormone Action

Hormones bind to membrane and nuclear receptors and act as the first messenger to trigger selective and diverse cellular responses. Membrane receptor binding (peptides and catecholamines) initiates signal transduction via four families of receptors: G protein-coupled receptors, tyrosine kinase receptors, serine kinases, and cytokine receptor-linked kinases. These receptors activate a second messenger system which includes cyclic adenosine monophosphate (cAMP), protein kinases, cyclic guanosine monophosphate, and calcium.¹ Receptor binding in the nucleus (steroids, thyroid hormone, and vitamin D) regulates gene expression in the cytoplasm and nucleus to produce specific intracellular proteins and enzymes.

Hypothalamus and Pituitary Gland

The hypothalamus is located at the base of the brain and above the pituitary gland. It receives input from multiple avenues to maintain homeostasis and affect growth and reproduction. Environmental factors such as light and temperature, autonomic inputs, adrenergic and dopaminergic receptors, pain signals, emotions, olfactory sensations, and peripheral endocrine organ feedback stimulate the hypothalamus to secrete hypothalamic-releasing and hypothalamic inhibitory hormones, which, in turn, control secretions from the anterior pituitary ([Table 37.1](#)).

TABLE 37.1

Hypothalamic hormones

Hormone	Target anterior pituitary hormone
Human growth hormone–releasing hormone	HGH
Human growth hormone–inhibiting hormone (somatostatin)	HGH, prolactin, TSH
Prolactin-releasing factor	Prolactin
Prolactin-inhibiting factor	Prolactin
Luteinizing hormone–releasing hormone	LH, FSH

Corticotropin-releasing hormone	ACTH, β -lipotropins, endorphins
Thyrotropin-releasing hormone	TSH

Abbreviations: ACTH, adrenocorticotrophic hormone; FSH, follicle-stimulating hormone; HGH, human growth hormone; LH, luteinizing hormone; TSH, thyroid-stimulating hormone.

Hormones designated as hypothalamic-releasing or hypothalamic inhibitory hormones originate in the hypothalamus and control secretions from the anterior pituitary ([Table 37.1](#)). Hypothalamic-releasing and inhibitory hormones travel via hypothalamic-hypophyseal portal vessels, which directs these hormones from a capillary bed in the hypothalamus directly to the anterior pituitary, without being diluted in the systemic circulation. When this high concentration of hormones reaches the pituitary, they bind G protein-coupled receptors and activate the cAMP second messenger system which subsequently leads to pituitary hormone release. Hypothalamic hormones have pulsatile secretion, which is superimposed on broader biologic rhythms such as the circadian release of adrenocorticotrophic hormone (ACTH), the sleep-entrained release of human growth hormone (HGH), and the monthly cycle of gonadotropins in females.²

The pituitary gland lies in the sella turcica at the base of the brain and is connected to the hypothalamus by the pituitary stalk. Physiologically, the gland is outside the blood-brain barrier and is divided into the anterior pituitary (adenohypophysis), derived from the embryological upper part of the gastrointestinal tract, and posterior pituitary (neurohypophysis), derived from neural tissue. The anterior pituitary synthesizes, stores, and secretes five tropic hormones that act on a secondary endocrine organ to secrete their own hormones. The ACTH and HGH are polypeptides; thyroid-stimulating hormone (TSH), luteinizing hormone (LH), and follicle-stimulating hormone (FSH) are glycoproteins, with a common α subunit and specific β subunit. The ACTH is derived from proopiomelanocortin, which is cleaved to create melanocyte-stimulating hormone, a pigment hormone that also plays a role in host immune response, and β -endorphin, which binds opioid receptors to produce pain relief.³ The posterior pituitary stores and secretes two hormones—arginine vasopressin (AVP), formerly designated antidiuretic hormone, and oxytocin. Both are initially synthesized in the hypothalamus and subsequently transported (via axons) to the posterior pituitary ([Table 37.2](#)). During the perioperative period, secretion of pituitary hormones increases with activation of the sympathetic nervous system.⁴

TABLE 37.2

Pituitary hormones

Hormone	Cell type	Principal action
Anterior pituitary		
Human growth hormone (somatotropin)	Somatotropes	Accelerates body growth; insulin antagonism
Prolactin	Lactotropes	Stimulates secretion of milk and maternal behavior; inhibits ovulation
Luteinizing hormone	Gonadotropes	Stimulates ovulation in females and testosterone secretion in males
Follicle-stimulating hormone	Gonadotropes	Stimulates ovarian follicle growth in females and spermatogenesis in males
Adrenocorticotrophic hormone	Corticotropes	Stimulates adrenal cortex secretion and growth; steroid production
Thyroid-stimulating hormone	Thyrotropes	Stimulates thyroid secretion and growth
β -Lipotropin	Corticotropes	Precursor of endorphins
Posterior pituitary		
Arginine vasopressin	Supraoptic nuclei	Promotes water retention and regulates plasma osmolarity
Oxytocin	Paraventricular nuclei	Causes ejection of milk and uterine contraction

The response to pituitary stalk destruction differs in the anterior and posterior pituitary gland. Stalk destruction causes axonal atrophy and subsequent loss of posterior pituitary function. After stalk destruction, the anterior pituitary can still respond to hypothalamic hormones in the peripheral blood via the inferior hypophyseal artery.

Anterior Pituitary

Anterior pituitary cells have been traditionally classified on the basis of their staining characteristics as agranular chromophobes or granular chromophils. Chromophils are subdivided into acidophils and basophils depending on the staining response to acidic or basic dyes. With more modern techniques, including electron microscopy and immunochemistry, it is possible to identify at least five types of cells, some of which secrete more than one tropic hormone (see [Table 37.2](#)).

Growth Hormone (Somatotropin)

Growth hormone (GH) is the most abundant anterior pituitary hormone. The GH stimulates growth of all tissues in the body and evokes intense metabolic effects ([Figure 37.1](#)).⁵ The most striking and specific effect is stimulation of linear bone growth that results from direct GH action on the epiphyseal cartilage plates of long bones. The GH indirectly stimulates growth through upregulation of insulin-like growth factor expression from the liver and local tissues. Excess secretion of GH before epiphyseal closure occurs causes gigantism. When GH secretion is excessive after epiphyseal closure and long bones can no longer increase in length but only in thickness, acromegaly results. The metabolic effects of GH include increased rates of protein synthesis (anabolic effect), increased mobilization of free fatty acids (ketogenic effect), antagonism of insulin action (diabetogenic effect), and sodium and water retention.

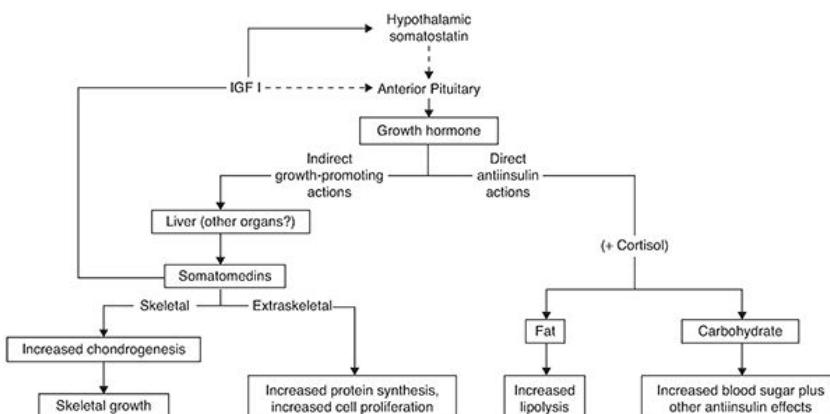


FIGURE 37.1 Effects of human growth hormone manifesting as direct effects or via production of somatomedins in the liver. Abbreviation: IGF I, insulin-like growth factor 1. Republished with permission of McGraw Hill LLC from Ganong WF. Review of Medical Physiology. 21st ed. New York, NY: Lange Medical Books/McGraw Hill, 2003; permission conveyed through Copyright Clearance Center, Inc.

Releasing (GH-releasing hormone) and inhibitory (somatostatin) hormones, physiologic events, and medications regulate GH secretion ([Table 37.3](#)). For example, perioperative anxiety and stress may evoke the release of GH.⁴ Plasma concentrations of GH characteristically increase during physiologic sleep. Drugs may influence the secretion of GH, presumably via effects on the hypothalamus. In this regard, large doses of corticosteroids suppress secretion of GH, which may be responsible for the inhibitory effects on growth observed in children receiving high doses of corticosteroids for prolonged periods of time. Conversely, dopaminergic agonists acutely increase the secretion of GH.

TABLE 37.3
Regulation of growth hormone (GH) secretion

Stimulation	Inhibition
GH-releasing hormone	GH-inhibiting hormone (somatostatin)
Stress	
Physiologic sleep	IGF-1
Hypoglycemia	
Free fatty acid decrease	Pregnancy
Amino acid increase	Hyperglycemia
Fasting	Free fatty acid increase
Estrogens	Cortisol
Dopamine	Obesity
α -Adrenergic agonists	

Abbreviation: IGF-1, insulin-like growth factor 1.

Prolactin

Prolactin is a nontropic hormone and has little metabolic activity, but it prompts the growth and development of the mammary gland and breast milk production itself. Pregnancy, via elevated levels of estrogen, nursing, and stress, stimulates the release of prolactin; dopamine inhibits its release ([Table 37.4](#)). Preoperative anxiety is an example of stress which increases plasma concentrations of prolactin.⁴ Prolactin secretion in response to suckling inhibits ovarian function, explaining the usual lack of ovulation and resulting infertility during breast-feeding. Prolactin also plays a role in the immune system, modulating immune cell activation and differentiation. Although not fully elucidated, high prolactin levels have been shown to be associated with autoimmune diseases like lupus, rheumatoid arthritis, and multiple sclerosis.⁶

TABLE 37.4

Regulation of prolactin secretion

Stimulation	Inhibition
Prolactin-releasing factor	Prolactin-inhibiting factor
Pregnancy	Prolactin
Suckling	Dopamine
Stress	L-Dopa
Physiologic sleep	
Metoclopramide	
Cimetidine	
Opioids	
α -Methyldopa	

Gonadotropins

The LH and FSH are gonadotropins responsible for pubertal maturation and secretion of steroid sex hormones by the gonads of either sex. These hormones bind to G protein-coupled cell membrane receptors in the ovaries or testes to stimulate the synthesis of cAMP, which then influences the production of sex steroids and triggers ovulation in females.

Adrenocorticotrophic Hormone

The ACTH regulates secretion of cortisol and androgens from the adrenal cortex via the cAMP second messenger system, which isolates cholesterol from lipid droplets. Cholesterol is the initial building block for the synthesis of corticosteroids. Secretion of ACTH is under the control of corticotropin-releasing hormone from the hypothalamus and conversely gets negative feedback from the circulating plasma concentration of

cortisol ([Table 37.5](#)).⁷ Secretory rates of corticotropin-releasing hormone and ACTH are high in the morning and low in the evening. This diurnal variation results in high plasma cortisol concentrations in the morning (~20 µg/dL) and low levels (~5 µg/dL) around midnight. For this reason, plasma concentrations of cortisol are interpreted in terms of the time of day of the measurement. Stress, surgical incision, reversal of anesthesia, and postoperative pain stimulate ACTH release.^{4,8,9}

TABLE 37.5

Regulation of adrenocorticotropic hormone (ACTH) secretion

Stimulation	Inhibition
Corticotropin-releasing hormone	ACTH
Cortisol decrease	Cortisol increase
Stress	Opioids
Sleep-wake transition	Etomidate
Hypoglycemia	Suppression of the hypothalamic-pituitary axis
Trauma	
α-Adrenergic agonists	
β-Adrenergic antagonists	

In the absence of ACTH, the adrenal cortex undergoes atrophy, but the zona glomerulosa, which secretes aldosterone under the influence of potassium and renin, is least affected. Indeed, hypophysectomy has minimal effects on electrolyte balance because of the continued release of aldosterone from the adrenal cortex. Pigmentary changes that may accompany certain endocrine diseases most likely reflect changes in plasma concentrations of ACTH, as it is derived from proopiomelanocortin, which also creates melanocyte-stimulating hormone. For example, pallor is a hallmark of hypopituitarism. Conversely, hyperpigmentation in patients with adrenal insufficiency from primary adrenal gland disease reflects high concentrations of ACTH circulating in plasma as the anterior pituitary attempts to stimulate corticosteroid secretion.

Chronic administration of corticosteroids suppresses corticotropin-releasing hormone and leads to atrophy the hypothalamic-pituitary axis. Several months may be required for recovery of this axis after removal of the suppressive influence. In such patients, stressful events during the perioperative period might evoke life-threatening hypotension. For this reason, it is a common practice to administer supplemental exogenous corticosteroids (based on the magnitude of stress) to patients considered at risk for suppression of the hypothalamic-pituitary axis. There is little evidence, however, that supplemental corticosteroids in excess of normal daily physiologic secretion are necessary or beneficial intra- or postoperatively.¹⁰ It is also unclear when the hypothalamic-pituitary-adrenal (HPA) axis is considered suppressed although general consensus is noted as taking more than 20 mg prednisone or its equivalent daily for greater than 3 weeks. See [Chapter 40](#) for dosing of corticosteroids during the perioperative period.

Thyroid-Stimulating Hormone

The TSH accelerates all the steps in the formation of thyroid hormones, including initial uptake of iodide into the thyroid gland, iodination of thyroglobulin, and internalization of thyroglobulin, which is needed to release thyroid hormone into blood. Secretion of TSH from the anterior pituitary is under the control of thyrotropin-releasing hormone from the hypothalamus as well as a negative feedback mechanism, depending on the concentrations of thyroid hormones circulating in plasma. Sympathetic nervous system stimulation and corticosteroids also suppress the secretion of TSH and thus diminish activity of the thyroid gland.

A long-acting thyroid stimulator is an immunoglobulin A antibody that binds to receptor sites on thyroid cells. Binding can mimic the effects of TSH and account for hyperthyroidism, and patients with hyperthyroidism often have detectable circulating concentrations of these proteins. Hypothyroidism with increased plasma concentrations of TSH indicates a primary defect at the thyroid gland (primary hypothyroidism) and an attempt by the anterior pituitary to stimulate hormonal output by releasing TSH. A

defect at the hypothalamus or anterior pituitary is indicated by low concentrations of both TSH and thyroid hormones circulating in plasma (secondary hypothyroidism).

Posterior Pituitary

The posterior pituitary acts as a reservoir for AVP and oxytocin in neurosecretory vesicles. The AVP is synthesized in the supraoptic nuclei and oxytocin in the paraventricular nuclei. These hormones are transported in secretory granules along axons from corresponding nuclei in the hypothalamus to the posterior pituitary for subsequent release in response to appropriate stimuli.

Arginine Vasopressin

The physiologic functions of AVP include vasoconstriction, water retention and corticotropin secretion. Changes in plasma osmolality and blood pressure are the main regulators of AVP secretion. The hypothalamus releases AVP to the posterior pituitary in response to feedback from osmoreceptors, which sense small changes in plasma osmolality, and aortic arch and carotid baroreceptors, which detect changes in blood pressure ([Table 37.6](#)).¹¹ Other inducers of AVP include stress and painful stimuli from surgery. Adequate hydration before induction of anesthesia can help blunt that response and maintain urine output. On the other hand, with general and/or epidural anesthesia and especially in patients taking ACE inhibitors, vasopressin becomes a vital factor in maintaining blood pressure since the sympathetic system and renin system are dampened.¹² Decreases in urine output and fluid retention previously attributed to release of AVP during positive pressure ventilation of the lungs are more likely the result of changes in cardiac filling pressures that impair the release of atrial natriuretic hormone.

TABLE 37.6

Regulation of arginine vasopressin secretion

Stimulation	Inhibition
Increased plasma osmolarity	Decreased plasma osmolarity
Hypovolemia	
Pain	Ethanol
Hypotension	α -Adrenergic agonists
Hyperthermia	Cortisol
Stress	Hypothermia
Nausea and vomiting	
Opioids	

There are three subtypes of AVP receptors: V1, V2, and V3. Stimulation of V1 receptors (found on vascular smooth muscle) causes vasoconstriction. In cases of hemorrhage and sepsis, large amounts of endogenous vasopressin are released initially, causing vasoconstriction and blood flow to be diverted from nonvital to vital organs. In continued refractory septic shock or cardiogenic shock, endogenous levels of vasopressin drop.¹² Thus, exogenous AVP is used as a vasopressor during intraoperative hypotension, sepsis, and cardiopulmonary resuscitation.

Activation of the V2 receptors, which are located on collecting duct cells in the kidney, increases reabsorption of water. The AVP is transported in the blood to the kidneys, where it attaches to receptors on the capillary side of epithelial cells lining the distal convoluted renal tubules and collecting ducts of the renal medulla. The receptor-hormone interaction results in the formation of large amounts of cAMP, which causes insertion of aquaporin-2 into the collecting duct walls for exit of water to minimize osmolality. Hypokalemia, hypercalcemia, cortisol, and lithium also interfere with renal responsiveness to AVP. The AVP binds to V3 receptors in the adenohypophysis to release corticotropin, which suggests that this hormone affects the stress response.¹¹

Destruction of neurons in or near the supraoptic and paraventricular nuclei of the hypothalamus from pituitary surgery, trauma, cerebral ischemia, or malignancy may decrease vasopressin release to cause central

diabetes insipidus.¹¹ If the posterior pituitary alone is damaged, however, the transected fibers of the pituitary stalk can still continue to secrete AVP. Diabetes insipidus from lack of vasopressin release during pituitary surgery is usually transient. (See [Chapter 40](#) for hormonal treatment of central diabetes insipidus.)

Unnecessary or excessive secretion of AVP with subsequent retention of water and dilutional hyponatremia may result from head injuries, intracranial tumors, meningitis, certain medications, or pulmonary infections. Aberrant production of AVP is observed most commonly in patients with cancer, especially small cell lung cancer. In cancer patients, the antibiotic demeclocycline promotes diuresis by antagonizing the effects of AVP on renal tubules.

Oxytocin

Breast suckling and cervical and vaginal stimulation, as from the fetus during labor, increases oxytocin secretion. Oxytocin causes milk ejection from the lactating mammary gland via contraction of the myoepithelial cells that surround the alveoli of the mammary glands. Oxytocin binds to G proteins on the surface of uterine myocytes to trigger the release of calcium from the sarcoplasmic reticulum, exerting a contracting effect on the pregnant uterus.¹³ Oxytocin also augments the action potential of the uterine smooth muscle.¹⁴ Large amounts of oxytocin cause sustained uterine contraction as necessary for postpartum hemostasis. Oxytocin has only 0.5% to 1.0% the antidiuretic activity of AVP and can be released abruptly and independently of AVP.

Thyroid Gland

Anatomically, the thyroid gland consists of two lobes connected by a bridge of tissues known as the **thyroid isthmus** ([Figure 37.2](#)). The gland is highly vascularized and receives innervation from the autonomic nervous system. Structurally, the gland consists of multiple follicles (acini) that are filled with colloid, which consists principally of thyroglobulin. Thyroid hormones are stored in combination with thyroglobulin. Stimulation of proteases by TSH results in cleavage of hormones from thyroglobulin and their release into the systemic circulation.

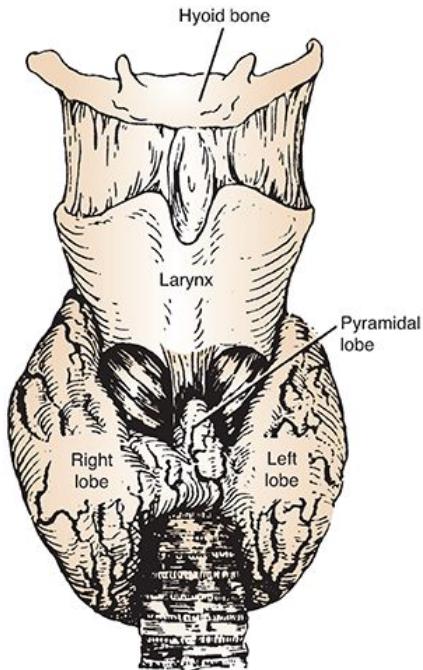


FIGURE 37.2 The two lobes of the thyroid and their relationship to the larynx and trachea.

The thyroid gland maintains optimal metabolism for normal tissue function.¹⁵ The principal hormonal secretions of the thyroid gland are thyroxine (T₄) and triiodothyronine (T₃) ([Figure 37.3](#)). The T₄, a

prohormone synthesized from tyrosine, represents 80% of the body's thyroid hormone production. The T₃, 5 times more active than T₄, is produced directly from tyrosine metabolism or from conversion of T₄ in peripheral tissues (mostly liver but also heart, muscle, nerves, intestines). This conversion is done by D1 or D2 deiodinases, which convert one-third of all T₄ into T₃. These deiodinases also further metabolize T₄ and T₃ to inactive compounds. The half-lives of endogenously or exogenously administered T₃ and T₄ are 1.5 and 7 days, respectively. The T₃ and T₄ are both highly protein bound to albumin, thyroid-binding prealbumin, and thyroid-binding globulin with only 0.2% of T₃ and 0.3% of T₄ freely circulating unbound and pharmacologically active.¹⁵ It is of interest that iodine present in thyroid hormones is not necessary for biologic activity (see [Figure 37.3](#)). In addition to thyroid hormones, the thyroid gland secretes calcitonin, which is important for calcium ion use.

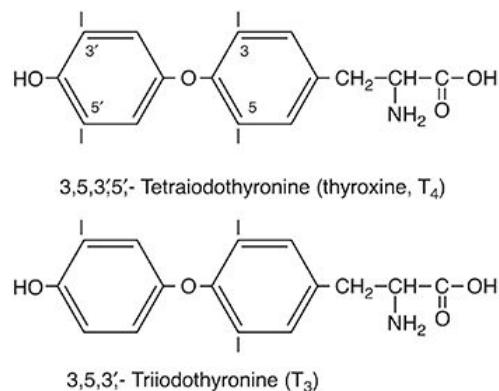


FIGURE 37.3 Chemical structure of thyroid hormones.

The thyroid hormones increase oxygen consumption in nearly all tissues, except for the brain, testicles, lymph nodes, and spleen. Failure of thyroid hormones to greatly alter the oxygen consumption of the brain is consistent with the minimal changes in anesthetic requirements minimum alveolar concentration (MAC) that accompany hyperthyroidism or hypothyroidism.¹⁶ Cardiovascular changes are often the earliest clinical manifestations of abnormal thyroid hormone levels. Absence of thyroid gland hormones decreases minute oxygen consumption to approximately 40% less than normal; excesses of thyroid hormones can expand oxygen consumption as much as 100% more than normal. Thyroid hormones stimulate carbohydrate metabolism and facilitate the mobilization of free fatty acids. Despite the latter effect, plasma concentrations of cholesterol usually decrease, reflecting stimulation of low-density lipoprotein receptor synthesis by thyroid hormones.

Mechanism of Action

When thyroid hormones enter cells, T₃ binds to nuclear receptors. The T₄ also binds to these receptors but not as avidly. Indeed, T₄ serves principally as a prohormone for T₃ so that the biologic effects of T₄ are largely a result of its intracellular conversion to T₃.

Thyroid hormones exert most, if not all, of their effects through control of protein synthesis. Thyroid hormones activate the DNA transcription process in the cell nucleus to form new cell proteins and enzymes. Sympathomimetic effects that accompany thyroid hormone stimulation most likely reflect a greater sensitivity of β-adrenergic receptors to the release of T₄ and T₃, although this is controversial.

When thyroid hormones accelerate metabolism, tissues vasodilate and blood flow delivers necessary oxygen and carries away metabolites and heat. As a result, cardiac output often increases, but systemic blood pressure is unchanged because peripheral vasodilation offsets the impact of more blood flow. Excess protein catabolism associated with greater secretion of thyroid hormones is the mechanism behind skeletal muscle weakness characteristic of hyperthyroidism. The fine muscle tremor that accompanies hyperthyroidism stems

from the sensitivity of neuronal synapses in the area of the spinal cord that controls skeletal muscle tone. Diarrhea reflects additional motility in the gastrointestinal tract with excessive activity of the thyroid gland.

Calcitonin

Calcitonin, a polypeptide hormone secreted by the thyroid gland, decreases the concentration of calcium ions in plasma by weakening the activity of osteoclasts and strengthening the activity of osteoblasts. In the kidneys, calcitonin decreases tubular absorption of calcium and phosphates. A total thyroidectomy and subsequent absence of calcitonin, however, does not measurably influence the plasma concentration of calcium because of the predominance of parathyroid hormone (PTH).

Parathyroid Glands

The four parathyroid glands secrete PTH, an amino acid polypeptide that regulates plasma concentration of calcium ions. Secretion of PTH is inversely related to plasma ionized calcium concentration. Small declines in the plasma concentration of calcium ions stimulate the release of PTH. The PTH promotes mobilization of bone calcium (osteoclastic activity); enhances conversion of vitamin D to its active form, 1,25-dihydroxycholecalciferol, to increase gastrointestinal absorption of calcium; increases renal tubular absorption of calcium; and inhibits renal reabsorption of phosphate to increase calcium and to decrease phosphate concentrations in plasma.

The PTH exerts its effect on target cells in bones, renal tubules, and the gastrointestinal tract by stimulating the formation of cAMP. Because a portion of cAMP synthesized in the kidneys escapes into the urine, its assay serves as a measure of parathyroid gland activity.

Adrenal Cortex

The adrenal cortex secretes three major classes of corticosteroids: mineralocorticoids, glucocorticoids, and androgens. The precursor of all corticosteroids is cholesterol. More than 30 different corticosteroids have been isolated from the adrenal cortex, but only two are important: aldosterone, a mineralocorticoid, and cortisol, the principal glucocorticoid ([Table 37.7](#)). The corticosteroids are not stored in the adrenal cortex; the rate of synthesis determines the subsequent plasma concentration. Anatomically, the adrenal cortex is divided into three zones designated the (1) **zona glomerulosa** that secretes mineralocorticoids, (2) **zona fasciculata** that secretes glucocorticoids, and (3) **zona reticularis** that secretes androgens and estrogens.

TABLE 37.7

Physiologic effects of endogenous corticosteroids (mg)

	Daily secretion	Sodium retention ^a	Glucocorticoid effect ^a	Antiinflammatory effect ^a
Aldosterone	0.125	3,000	0.3	Insignificant
Desoxycorticosterone	—	100	0	0
Cortisol	20	1	1	1
Corticosterone	Minimal	15	0.35	0.3
Cortisone	Minimal	0.8	0.8	0.8

^aRelative to cortisol.

Mineralocorticoids: Aldosterone

Aldosterone accounts for approximately 95% of the mineralocorticoid activity of the corticosteroids. Desoxycorticosterone, the other naturally occurring mineralocorticoid, has only 3% of the sodium ion-retaining potency of aldosterone. Cortisol induces retention of sodium ions and secretion of potassium ions but much less effectively than aldosterone.

Physiologic Effects

Aldosterone sustains extracellular fluid volume by conserving sodium and by maintaining a normal plasma concentration of potassium. Sodium ions are absorbed at the same time potassium ions are secreted by the lining of epithelial cells of the distal renal tubules and collecting ducts. As a result, sodium is conserved in the extracellular fluid, and potassium is excreted in the urine. Water follows sodium such that extracellular fluid volume changes in proportion to the rate of aldosterone secretion. If aldosterone secretion is excessive, extracellular fluid volume, cardiac output, and systemic blood pressure increase. If plasma concentration of potassium decreases approximately 50% after excess secretion of aldosterone, skeletal muscle weakens or paralysis occurs because nerve and muscle membranes are hyperpolarized and the transmission of action potentials is prevented.

Aldosterone affects sweat glands and salivary glands. It increases the reabsorption of sodium and secretion of potassium by sweat glands. This effect conserves sodium in hot environments or during excess salivation. Aldosterone also enhances sodium ion reabsorption by the gastrointestinal tract.

Mechanism of Action

Aldosterone diffuses to the interior of renal tubular epithelial cells, where it induces DNA to form messenger RNA (mRNA) necessary for the transport of sodium and potassium ions. It is speculated that this mRNA is a specific adenosine triphosphatase that catalyzes energy from cytoplasmic adenosine triphosphate to the sodium ion transport mechanism of cell membranes. It takes as long as 30 minutes before the new mRNA appears and approximately 45 minutes before the rate of sodium ion transport begins to increase.

Regulation of Secretion

The most important stimulus for aldosterone secretion is an accumulation of potassium in the plasma. A powerful negative feedback system maintains the plasma concentration of potassium ions in a normal range. The renin-angiotensin system also affects aldosterone secretion (see [Chapter 16](#)). The elimination half-time of aldosterone is approximately 20 minutes, and nearly 90% is cleared by the liver in a single passage. Mineralocorticoid secretion is not under the primary control of ACTH. For this reason, hypoadosteronism does not accompany loss of ACTH secretion from the anterior pituitary.

Glucocorticoids: Cortisol

At least 95% of the glucocorticoid activity results from the secretion of cortisol. A small amount of glucocorticoid activity is provided by corticosterone and an even smaller amount by cortisone. Cortisol is one of the few hormones essential for life.

Physiologic Effects

Cortisol (1) increases gluconeogenesis, (2) breaks down protein, (3) mobilizes fatty acid, and (4) has antiinflammatory effects. Cortisol may improve cardiac function by increasing the number or responsiveness of β -adrenergic receptors. In addition to sustaining cardiac function and maintaining systemic blood pressure, cortisol promotes the normal responsiveness of arterioles to the constrictive action of catecholamines. Cortisol inhibits bone formation.

Developmental Changes

Plasma concentrations of cortisol increase progressively during the last trimester of pregnancy to reach a peak plasma concentration at term so that systems critical for survival are mature for the onset of extrauterine life. These systems include production of pulmonary surfactant, maturation of various enzyme systems in the liver, increased production of T_3 , and the expression of phenylethanolamine *N*-methyltransferase, the enzyme necessary for the synthesis of epinephrine from norepinephrine. The T_3 and catecholamines are both in preparation for the increase in metabolic rate associated with breathing and living in a colder environment.

Gluconeogenesis

Cortisol stimulates gluconeogenesis by the liver as much as 10-fold. Amino acids are mobilized from extrahepatic sites and transferred to the liver for conversion to glucose. An accelerated rate of

gluconeogenesis with a moderate decline in glucose use caused by a prolonged high level of cortisol can result in larger concentrations of blood glucose known as **adrenal diabetes**. Increased muscle wasting and thus decreased glucose utilization, insulin resistance, and visceral fat deposition (see the following text) associated with high cortisol levels also contribute to the development of diabetes. Adrenal diabetes may be responsive to the administration of insulin, but the overall cure is to treat the underlying cause of high cortisol.

Protein Catabolism

Cortisol breaks down protein stores in nearly all cells except hepatocytes to mobilize amino acids for gluconeogenesis. When excesses of cortisol are sustained, skeletal muscle weakness may become pronounced.

Fatty Acid Mobilization

Cortisol promotes mobilization of fatty acids from adipose tissue and enhances oxidation of fatty acids in cells. Despite these effects, with excess amounts of cortisol, fat is deposited in the neck and chest regions, giving rise to a “buffalo-like” torso. Fat deposits at these sites at a rate that exceeds its mobilization.

Antiinflammatory Effects

In large amounts, cortisol has antiinflammatory effects when it stabilizes lysosomal membranes and stops migration of leukocytes into the inflamed area. When lysosomal membranes are stable, the release of inflammation-causing lysosomes is attenuated. Cortisol lessens capillary permeability to prevent loss of plasma into tissues. Even after inflammation has been well established, the administration of cortisol weakens its manifestations. This effect of cortisol is useful for disease states with inflammation such as rheumatoid arthritis and acute glomerulonephritis.

Cortisol minimizes the number of eosinophils and leukocytes in the blood within a few minutes after its administration. Atrophy of lymphoid tissue throughout the body reduces the production of antibodies. As a result, the level of immunity against bacterial or viral infection is diminished, and infection can fulminate. Conversely, suppressing immunity is useful to prevent immunologic rejection of transplanted tissues.

In the treatment of allergic reactions, cortisol prevents the life-threatening inflammatory responses of allergic reactions such as laryngeal edema. Cortisol may also interfere with activation of the complement pathway and formation of chemical mediators derived from arachidonic acid, such as leukotrienes. Cortisol does not, however, alter the antigen-antibody interaction or histamine release associated with allergic reactions.

Mechanism of Action

Steroids are intracrine hormones that interact with intracellular (often nuclear) receptors. Cortisol stimulates DNA-dependent synthesis of mRNA in the nuclei of responsive cells, leading to the synthesis of necessary enzymes.

Regulation of Secretion

The most important stimulus for the secretion of cortisol (13–20 mg daily) is the release of ACTH from the anterior pituitary (see [Table 37.5](#)). The secretion of ACTH in the anterior pituitary is determined by two hypothalamic neurohormones: diurnal release of corticotropin-releasing hormone and AVP that act synergistically. Circulating cortisol has a direct negative feedback effect on the hypothalamus and anterior pituitary to decrease the discharge of corticotropin-releasing hormone and ACTH from these respective sites. Immediately following migration from the adrenal gland, cortisol is bound to the α -globulin, transcortin (cortisol-binding globulin). Plasma concentrations of cortisol are higher in females than in males with additional concentrations accompanying the menstrual cycle just before ovulation. If stress from the perioperative period overrides the normal negative feedback control mechanisms, plasma concentrations of cortisol increase. The beneficial effect of a greater plasma concentration of cortisol and other hormones in

response to stressful stimuli may be the acute mobilization of cellular proteins and fat stores for energy and synthesis of other compounds, including glucose.

Cortisol is secreted and released by the adrenal cortex at a basal rate of approximately 20 to 30 mg daily. In response to maximal stressful stimuli (sepsis, burns), the output of cortisol is increased to approximately 150 mg daily.¹⁷ This amount should be a sufficient replacement for patients who lack adrenal function and who are acutely ill or undergoing major surgery. The peak plasma cortisol concentration of 8 to 25 µg/dL occurs in the morning shortly after awakening. Stress-induced changes in the plasma concentration of cortisol are superimposed on the circadian tone and vary in onset, magnitude, and duration, depending on the intensity of the stress. In the systemic circulation, 80% to 90% of cortisol is bound to a specific globulin known as **transcortin**. It is the relatively small amount of unbound cortisol that exerts a biologic effect. The elimination half-time of cortisol is approximately 70 minutes. Cortisol is degraded mainly in the liver with the formation of inactive 17-hydroxycorticosteroids that appear in the urine. Cortisol is also filtered at the glomerulus and may be excreted unchanged in urine.

Effect of Anesthesia and Surgery

Perioperative stress stimulates hormonal secretion of ACTH and cortisol.⁴ This response may be diminished by less invasive surgeries such as laparoscopy and blunted by choice of anesthetic technique. During the perioperative period, ACTH stimulation, tissue damage, and proinflammatory mediators can release cortisol. As with other types of stress, the episodic release of cortisol remains intact but the amplitude of episodic releases is greater. Large concentrations of cortisol in plasma in the perioperative period may be prompted by baroreceptor and spinal reflexes that signal tissue injury to the hypothalamus.¹⁸

Plasma cortisol concentrations typically return to normal levels within 24 hours postoperatively but may remain elevated for as long as 72 hours, depending on the severity of the surgical trauma. In addition, disturbances in the circadian rhythm may be associated with postoperative fatigue and debility. Return of plasma cortisol concentrations to normal following surgery is characterized by increased plasma concentrations of ACTH and cortisol (consistent with sustained, stress-induced stimulation of the hypothalamus) followed by a second phase in which plasma ACTH concentrations are low and larger cortisol concentrations in plasma are independent of the hypothalamic-pituitary system. Cytokines released from traumatized tissue may stimulate synthesis of cortisol directly despite low plasma concentrations of ACTH. Alternatively, prior increases in ACTH concentrations in plasma may stimulate production of ACTH receptors in the adrenal glands resulting in greater cortisol production.

Plasma cortisol concentrations in the perioperative period are designed to provide protection during and after surgery. In adrenalectomized animals who received subphysiologic doses of cortisol, hemodynamic instability and mortality followed surgery. Animals treated with physiologic or supraphysiologic doses of cortisol were indistinguishable from control animals.¹⁹ A key feature of HPA physiology is negative feedback that suppresses release of ACTH by the pituitary by high levels of endogenous or exogenous glucocorticoids. Suppression of the hypothalamic-pituitary axis by regular administration of corticosteroids prevents the release of cortisol in response to stressful stimuli.

The acute phase response to surgery is also mediated by the release of proinflammatory cytokines such as interleukin-1, tumor necrosis factor- α , and interleukin-6 from damaged tissue and activation of the sympathetic nervous system. Cytokines may stimulate ACTH and cortisol production and are subject to a negative feedback system. Cytokine levels peak 24 hours after surgery and can remain elevated for several days. Hepatic production of acute phase proteins (C-reactive protein, fibrinogen, and α_2 -macroglobulin) is generated in response to trauma and surgery.⁴

In addition to surgical trauma, the choice of anesthetic drugs and techniques may influence the HPA response. Large doses of opioids may attenuate the cortisol response to surgical stimulation.^{20,21} Volatile anesthetics do not suppress the stress-induced endocrine response as much. Etomidate, unique among drugs administered to induce anesthesia, inhibits cortisol synthesis even in the absence of surgical stimulation (see [Chapter 5](#)). Although studies of regional anesthetics show a potential to decrease perioperative complications and surgical stress-induced release of cortisol, it has not been proven in abdominal or thoracic surgeries.

Reproductive Glands

In both sexes, the reproductive glands (testes and ovaries) produce germ cells and steroid sex hormones.

Testes

The testes have two main products: **androgens** and sperm. All androgens are steroid compounds that can be synthesized from cholesterol. Testosterone, the most potent and abundant of the androgens, is a key factor in primary sexual development (spermatogenesis, testicular descent, enlargement of penis and testes, increasing libido) and develops and maintains male sex characteristics. Skeletal muscle growth is an anabolic effect of testosterone in the male. Puberty is characterized by the production of testosterone rapidly in response to hypothalamic-releasing hormones that evoke the release of LH and FSH. Hypertrophy of the laryngeal mucosa accompanies secretion of testosterone, leading to changes in voice at puberty. Testosterone increases secretion of sebaceous glands, leading to acne. Testosterone causes growth spurts by increasing tissue growth at epiphyseal plates. Beard growth is the last manifestation of puberty.

The hypothalamic-pituitary axis regulates testosterone production. Gonadotropin-releasing hormone is released from the hypothalamus and causes secretion of LH and FSH from the anterior pituitary. The LH acts on Leydig cells in the gonads to increase testosterone production. The FSH and androgens act on receptors in Sertoli cells to stimulate spermatogenesis. Testosterone is part of a negative feedback loop to the hypothalamus and anterior pituitary. Testosterone production continues throughout life, although the amount produced lessens gradually after 40 years. At age 80 years, it is approximately one-fifth the peak value.

At most sites of action, testosterone is not the active form of the hormone. It is converted in target tissues to the more active dihydrotestosterone by a reductase enzyme. Dihydrotestosterone binds to a cytoplasmic protein receptor for synthesis of specific mRNA protein. In the absence of sufficient reductase enzyme, external genitalia fail to develop (pseudohermaphroditism) despite secretion of adequate amounts of testosterone. Not all target tissues, however, require the conversion of testosterone to dihydrotestosterone for activity. For example, effects of testosterone on skeletal muscles and bone marrow are mediated by the hormone or a metabolite other than dihydrotestosterone.

The adrenal cortex also secretes androgens, but the effects of these hormones are usually inconsequential unless a hormone-secreting tumor develops. For example, in males, approximately 10% of androgens are produced in the adrenal cortex, an insufficient amount to maintain spermatogenesis or secondary sexual features in an adult male. In abnormal conditions, such as the adrenogenital syndrome, the adrenal cortex can secrete large quantities of steroids and androgenic precursors.

Ovaries

The two ovarian hormones, estrogen and progesterone, are secreted in response to LH and FSH, which are released from the anterior pituitary in response to hypothalamic-releasing hormones. In postpubertal females, an orderly secretion of LH and FSH is necessary for menstruation, pregnancy, and lactation. The Stein-Leventhal syndrome is characterized by virilization when ovarian secretion of androgens is excessive.

Estrogens

Estrogens give the female sexual characteristics. In the nonpregnant female, most of the estrogen comes from the ovaries; small amounts are also secreted by the adrenal cortex. The three most important estrogens are β -estradiol, estrone, and estriol. These estrogens are conjugated in the liver to inactive metabolites that appear in urine.

Progesterone

Progesterone prepares the uterus for pregnancy and the breasts for lactation. Almost all of the progesterone in the nonpregnant female is secreted by the corpus luteum during the lateral phase of the menstrual cycle. The adrenal cortex forms small amounts of progesterone. Progesterone is metabolized to pregnanediol, which appears in the urine and is a valuable index of the secretion and metabolism of this hormone.

Menstruation

The overall duration of a normal menstrual cycle is 21 to 35 days and consists of three phases designated as follicular, ovulatory, and luteal. The follicular phase begins with the onset of menstrual bleeding after the plasma concentration of progesterone decreases. After a variable length of time, the follicular phase is followed by the ovulatory phase lasting 1 to 3 days and culminating in ovulation. The increase in body temperature ($\sim 0.5^{\circ}\text{C}$) that accompanies ovulation most likely reflects a thermogenic effect of progesterone. The luteal phase follows ovulation and is characterized by the development of a corpus luteum that secretes progesterone and estrogen. The corpus luteum degenerates after a fairly constant period of 13 to 14 days, and the menstrual cycle repeats.

Pregnancy

During pregnancy, the placenta forms large amounts of estrogens, progesterone, chorionic gonadotropin, and chorionic somatomammotropin. Chorionic gonadotropin prevents the usual involution of the corpus luteum or the onset of menstrual bleeding. The first key hormone of pregnancy, chorionic gonadotropin, which can be detected in the maternal plasma within 9 days after conception, is the basis for pregnancy tests. After approximately 12 weeks, the placenta secretes sufficient amounts of progesterone and estrogens to maintain pregnancy and the corpus luteum involutes. Chorionic somatomammotropin attenuates insulin activity, making more glucose available to the fetus.

Circulating concentrations of estrogen enlarge the breasts and uterus; progesterone is necessary to develop decidual cells in the uterine endometrium and to suppress uterine contractions that could result in spontaneous abortion. Greater concentrations of progesterone in plasma and associated sedative effects during pregnancy may explain why requirements for volatile anesthetics lessen in gravid animals. In animals, anesthetic requirements return to nonpregnant values within 5 days postpartum, whereas the plasma concentration of progesterone remains increased, suggesting that the decrease in MAC cannot be attributed entirely to progesterone.²² Progesterone increases carbon dioxide sensitivity in central respiratory centers, which is the stimulus for increased alveolar ventilation that accompanies pregnancy. Near term, the ovaries secrete the hormone relaxin, which relaxes pelvic ligaments, so the sacroiliac joints become limber and the symphysis pubis becomes elastic.

The parturient with asthma may experience unpredictable changes in airway reactivity. Exacerbation of asthma from bronchoconstriction is evoked by prostaglandins of the F series, which are present in all trimesters of pregnancy but especially during labor. Conversely, prostaglandins of the E series are bronchodilators and predominate during the third trimester. That corticosteroids alter airway responsiveness is questionable because the plasma concentrations of cortisol associated with pregnancy are offset by the carrier protein transcortin, with the net effect being an unchanged level of available cortisol.

Menopause

Between the ages of 45 and 55 years, a woman's ovaries gradually become unresponsive to the stimulatory effects of LH and FSH, and the sexual cycles disappear. Because the negative feedback control of estrogen and progesterone on the anterior pituitary is decreased, output of LH and FSH accumulates in circulating plasma concentrations. Sensations of warmth spreading from the trunk to the face (hot flashes) coincide with surges of LH secretion and are prevented by exogenous administration of estrogens.

Pancreas

The exocrine pancreas secretes digestive substances into the duodenum. The islets of Langerhans are organized endocrine cells that secrete four hormones (insulin, glucagon, somatostatin, and pancreatic polypeptide) into the systemic circulation. The pancreas contains 1 to 2 million islets, which, based on staining characteristics and morphology, are classified as α , β , δ , and pancreatic polypeptide cells.²³ β Cells account for about 60% of the islet cells and are the site of insulin production. The α cells account for 25% of islet cells and produce glucagon. Each islet receives a generous blood supply, which, unlike any other endocrine organ, drains into the portal vein.

Insulin

Insulin is a 51-amino acid peptide hormone synthesized in the β cells of the islets of Langerhans as a single polypeptide proinsulin, which is the precursor molecule to insulin (Figure 37.4).^{24,25} The peptide that connects the amino terminus of the A chain to the carboxyl terminus of the B chain is designated the connecting (C) peptide. Proinsulin is converted to insulin and C-peptide, and these two molecules are stored together in secretory granules. When pancreatic β cells are stimulated, equimolar amounts of insulin C-peptide are released. Thus, plasma concentrations of insulin C-peptide reflect functional activity of pancreatic β cells. Insulin is an anabolic hormone promoting the storage of glucose, fatty acids, and amino acids (Figure 37.5).²⁶ The amount of insulin secreted daily is equivalent to approximately 40 units. In the systemic circulation, insulin has an elimination half-time of approximately 5 minutes, with greater than 80% degraded in the liver and kidneys.

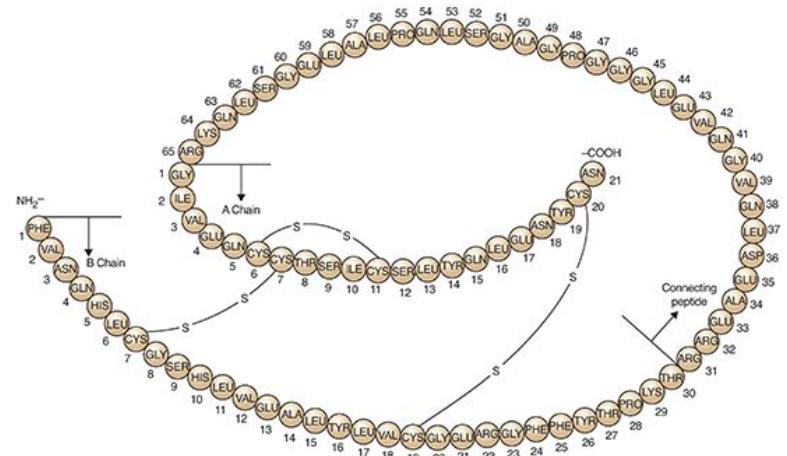


FIGURE 37.4 Proinsulin, which is converted to insulin by proteolytic cleavage of amino acids 31, 32, 64, 65, and the connecting peptide. Republished with permission of McGraw Hill LLC from Larner J. *Insulin and oral hypoglycemic drugs: glucagon*. In: Gilman AG, Goodman LS, Rall TW, et al., eds. The Pharmacological Basis of Therapeutics. 7th ed. New York, NY: MacMillan; 1985; permission conveyed through Copyright Clearance Center, Inc.

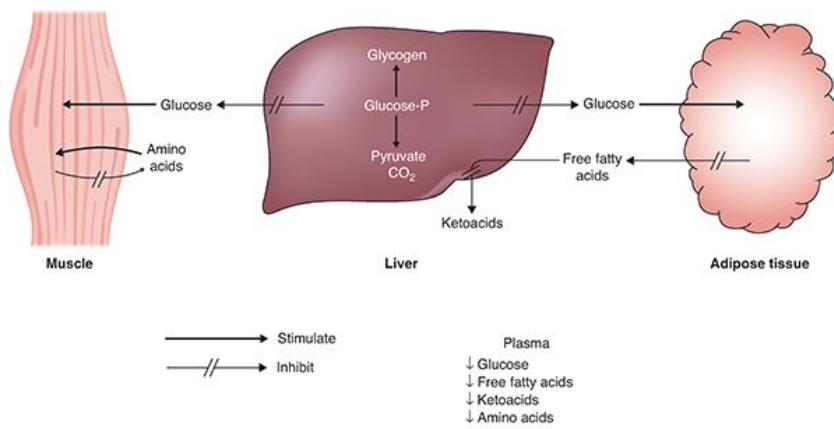


FIGURE 37.5 Insulin stimulates tissue uptake of glucose and amino acids, whereas release of fatty acids is inhibited. As a result, the plasma concentrations of glucose, free fatty acids, amino acids, and ketoacids decrease. *From Berne RM, Levy MN, Koeppen BM, et al. Physiology. 5th ed. St Louis, MO: Mosby; 2004.* Reprinted with permission from Bruce M. Koeppen, MD.

Insulin binds to a transmembrane, glycoprotein receptor with two distinct insulin-binding domains (an extracellular domain of α subunits and an intracellular domain of β subunits) to regulate metabolic function.

When insulin binds to the extracellular domain, a conformational change of the α subunits facilitates adenosine triphosphate binding to the β subunits. As a result, tyrosine molecules in the intracellular portions of the transmembrane receptors are autophosphorylated. The phosphorylated receptor phosphorylates other protein substrates such as insulin receptor substrates that mediate enzyme activation (mitogen-activated protein), inactivation, and metabolic signaling (Figure 37.6).⁹ The insulin cascade stimulates translocation of glucose transporters (glucose transporter type 4) from the cytosol to plasma membranes to (1) facilitate glucose diffusion into cells; (2) shift intracellular glucose metabolism toward glycogen storage via glycogen synthetase activation; (3) stimulate cellular uptake of amino acids, phosphate, potassium, and magnesium; (4) stimulate protein synthesis and inhibit proteolysis; and (5) regulate gene expression via insulin regulatory elements in target DNA molecules. Activation of sodium-potassium adenosine triphosphatase in cell membranes by insulin moves potassium ions into cells and decreases concentration of potassium in plasma.

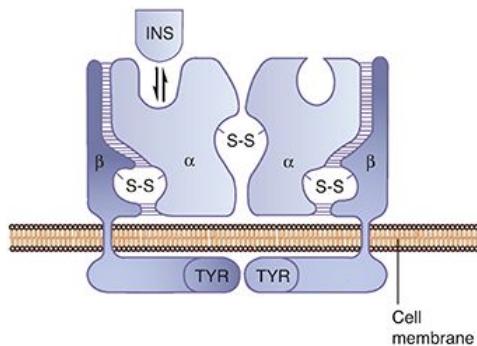


FIGURE 37.6 Schematic depiction of the insulin receptor consisting of two α and two β subunits joined by disulfide bonds ($-S-S-$). Insulin (INS) attaches to the α subunits, which triggers autophosphorylation of the tyrosine kinase (TYR) portions of the β subunits inside the cell and the resultant effects of insulin.

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Regulation of Secretion

The principal control of insulin secretion is via a negative feedback effect of the blood glucose concentration in the pancreas (Table 37.8). Virtually no insulin is secreted by the pancreas when the blood glucose concentrations are less than 50 mg/dL, and maximum stimulation for release of insulin is at concentrations greater than 300 mg/dL. Thus, blood glucose concentrations are maintained within a narrow range. The pancreas is richly innervated by the autonomic nervous system so that insulin is released in response to β -adrenergic stimulation or to acetylcholine. Conversely, α -adrenergic stimulation or β -adrenergic blockade inhibits insulin release. Oral glucose is more effective than glucose administered intravenously in evoking the release of insulin, suggesting the presence of an anticipatory signal from the gastrointestinal tract to the pancreas. Glycosuria is more likely after intravenous rather than oral glucose administration. Glucagon, HGH, and corticosteroids potentiate glucose-induced stimulation of insulin secretion. Prolonged secretion of these hormones or their exogenous administration can exhaust pancreatic β cells and lead to diabetes mellitus. Indeed, diabetes mellitus is found in patients who develop acromegaly or in individuals with a diabetic tendency who are treated with corticosteroids.

TABLE 37.8

Regulation of insulin secretion	
Stimulation	Inhibition
Hyperglycemia	Hypoglycemia
β -Adrenergic agonists	β -Adrenergic antagonists
Acetylcholine	α -Adrenergic agonists

Glucagon	Somatostatin
	Diazoxide
	Thiazide diuretics
	Volatile anesthetics
	Insulin

Physiologic Effects

Insulin receptor expression is highest in tissues, which regulate glucose, lipid, and protein metabolism (adipose, skeletal muscle, and liver) via insulin. Insulin promotes the use of carbohydrates for energy while depressing the use of fats and amino acids. For example, insulin facilitates storage of fat in adipose cells by inhibiting lipase enzyme, which normally hydrolyzes triglycerides in fat cells. In the liver, insulin inhibits enzymes necessary for gluconeogenesis, thus conserving amino acid stores.

Insulin facilitates glucose uptake and storage in the liver through effects on specific enzymes. When insulin induces the activity of glucokinase, uptake of glucose into liver cells is enhanced. Glucokinase is the enzyme that causes initial phosphorylation of glucose after it diffuses into hepatocytes. Once phosphorylated, glucose is trapped and unable to diffuse back through cell membranes. Storage is further enhanced by insulin-induced inhibition of phosphorylase enzyme, which normally causes liver glycogen to split into glucose. The net effects of these actions of insulin on enzymes is to increase hepatic stores of glycogen up to a maximum of approximately 100 g. Ordinarily, approximately 60% of the glucose in a meal is stored in the liver as glycogen.

Resting skeletal muscles are almost impermeable to glucose except in the presence of insulin. Glucose that enters resting skeletal muscles under the influence of insulin is stored as glycogen for subsequent use as energy. The amount of glycogen that can be stored in skeletal muscles, however, is much less than the amount that can be stored in the liver. Furthermore, glycogen in skeletal muscles, unlike that stored in the liver, cannot be reconverted to glucose and released into the systemic circulation because skeletal muscles lack glucose phosphatase enzyme, which is necessary for splitting glycogen. Exercise increases the permeability of skeletal muscle membranes to glucose, perhaps because insulin is released from within the skeletal muscle itself or its vasculature.

Brain cells are unique in that the permeability of their membranes to glucose does not depend on the presence of insulin. This characteristic is crucial because brain cells use only glucose for energy, thus the importance of maintaining blood glucose concentrations above a critical level of approximately 50 mg/dL. Indeed, lack of insulin causes the use mainly of fat for energy to the exclusion of glucose, except by brain cells.

Deficiencies in insulin signaling are associated with insulin resistance. When an impaired intracellular signal decreases recruitment of proteins that transport glucose to the plasma membrane for glucose uptake, an individual is said to have insulin resistance. Compensatory hyperinsulinemia overcomes peripheral tissue resistance to insulin. A feedback loop exists between insulin responsiveness in target tissues and insulin secretion by pancreatic β cells.

Glucagon

Glucagon is a catabolic hormone acting to mobilize glucose, fatty acids, and amino acids into the systemic circulation ([Figure 37.7](#)).²⁶ These responses are the reciprocal of the insulin effects, emphasizing that these two hormones are also reciprocally secreted ([Table 37.9](#)). Indeed, the principal stimulus for secretion of glucagon is hypoglycemia. Glucagon abruptly increases the blood glucose concentration by stimulating glycogenolysis in the liver. Glucagon activates adenylate cyclase for the subsequent formation of cAMP. The metabolic effects of glucagon at the liver mimic those produced by epinephrine. Indeed, the study of the mechanism by which glucagon and epinephrine act as hyperglycemics led to the discovery of cAMP.²⁷ Glucagon also causes hyperglycemia by stimulating gluconeogenesis in hepatocytes. Enhanced myocardial contractility and more secretion of bile are effects when exogenous administration increases plasma concentrations of glucagon far above normal levels. Amino acids help the release of glucagon and thus

prevent hypoglycemia from ingestion of a pure protein meal, which stimulates insulin secretion. Glucagon undergoes enzymatic degradation to inactive metabolites in the liver and kidneys and at receptor sites in cell membranes. The elimination half-time of glucagon is brief—only 3 to 6 minutes.

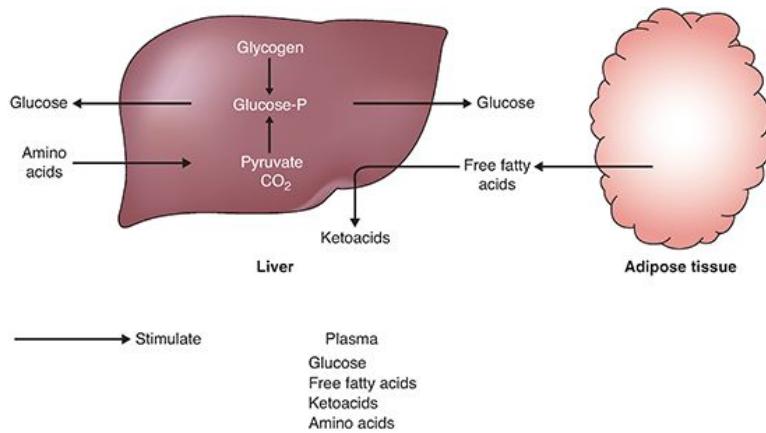


FIGURE 37.7 Glucagon stimulates tissue release of glucose, free fatty acids, and ketoacids and hepatic uptake of amino acids. *From Berne RM, Levy MN, Koeppen BM, et al. Physiology. 5th ed. St Louis, MO: Mosby; 2004. Reprinted with permission from Bruce M. Koeppen, MD.*

TABLE 37.9

Regulation of glucagon secretion

Stimulation	Inhibition
Hypoglycemia	Hyperglycemia
Stress	Somatostatin
Sepsis	Insulin
Trauma	Free fatty acids
β-Adrenergic agonists	α-Adrenergic agonists
Acetylcholine	
Cortisol	

Somatostatin

Somatostatin regulates islet cell secretion, inhibits both insulin and glucagon release, and inhibits several gastrointestinal processes including gallbladder contraction, gastric motility, and splanchnic blood flow.²⁸ This peptide is the same as GH-releasing inhibitory hormone that is secreted by the hypothalamus.

Pancreatic Polypeptide

Pancreatic polypeptide inhibits pancreatic exocrine secretion, gallbladder contraction, vagally stimulated gastric acid secretion, and gut motility.^{29–31}

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Drugs that Alter Glucose Regulation

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Diabetes Mellitus

According to recent recommendations by the American Diabetes Association and the World Health Organization, diabetes mellitus is classified by the underlying disease etiology (ie, type 1 vs type 2) rather than by age of onset (ie, juvenile-onset vs adult-onset diabetes) or treatment modality (ie, insulin-dependent vs non-insulin-dependent diabetes).¹ The insulin deficiency in type 1 diabetes is the result of autoimmune-mediated destruction of pancreatic β cells. Patients depend on exogenous insulin to regulate metabolism. Lack of insulin may precipitate diabetic ketoacidosis, a complex and potentially life-threatening metabolic derangement. Onset of type 1 diabetes is at a younger age than onset of type 2 diabetes, and sensitivity to insulin is normal. In type 2 diabetes, there is a failure to secrete insulin due to pancreatic β cell dysfunction that is coupled with peripheral insulin resistance. Oral hypoglycemic drugs are alternatives to exogenous administration of insulin to patients with type 2 diabetes. Most cases of diabetes are either type 1 or type 2 (approximately 90%); the remaining causes include gestation, exocrine pancreas disease, medications, endocrinopathies, genetic defects in insulin action and β cell function, infections, and uncommon immune-mediated disorders ([Table 38.1](#)).²

TABLE 38.1

Etiologic classification of diabetes mellitus

Type 1 diabetes mellitus (absolute insulin deficiency from pancreatic β cell destruction)
Type 2 diabetes mellitus (insulin resistance vs insulin deficiency)
Gestational diabetes mellitus
Exocrine pancreas disease (pancreatitis, pancreatectomy, cystic fibrosis, hemochromatosis)
Drug-induced (glucocorticoids, thiazides, thyroid hormone, β -adrenergic agonists)
Endocrinopathies (acromegaly, Cushing syndrome, glucagonoma)
Genetic defects in pancreatic β cell function
Genetic defects in insulin action (resistance)
Infections (congenital rubella, cytomegalovirus)
Uncommon immune-mediated diabetes (“stiff man” syndrome, anti-insulin receptor antibodies)

Under normal circumstances, insulin is released from pancreatic β cells in response to an increase in serum glucose. Insulin increases glucose uptake and use in fat and muscle and inhibits gluconeogenesis and glycogenolysis in the liver. In the setting of insulin deficiency and/or peripheral insulin resistance, hyperglycemia is caused by impaired glucose utilization, increased glycogenolysis, and generation of gluconeogenic precursors from peripheral muscle proteolysis with a subsequent increase in gluconeogenesis.

In the absence of insulin (as in type 1 diabetes), an increase in lipolysis and circulating free fatty acids leads to increased production of ketones in the liver, which serves as an energy source for skeletal muscles and cardiac muscles. Excess production of ketones can cause diabetic ketoacidosis. Urinary excretion of ketones contributes to the depletion of electrolytes, especially potassium. Hypokalemia, however, may not be apparent, because intracellular potassium ions are exchanged for extracellular ions to compensate for the acidosis.

When the primary pathology is peripheral insulin resistance and low serum levels of insulin are still present (as in type 2 diabetes), insulin may block lipolysis without preventing hyperglycemia. This explains why hyperglycemia can exist without the presence of ketone bodies. Ketosis can be reliably prevented by continuously providing all diabetic patients with glucose and insulin.³ Prevention is uniquely important in the perioperative period when nutritional intake is altered.

Hyperglycemia impairs vasodilation and induces a chronic proinflammatory, prothrombotic, and proatherogenic state and can cause vascular complications.⁴ Although all tissues are affected, the atherosclerotic changes that cause peripheral vascular disease, renal insufficiency, and cerebrovascular disease have the greatest impact on perioperative management.

The goals of therapy for patients with diabetes mellitus include preventing the adverse consequences of hypoglycemia and hyperglycemia, avoiding weight gain, and reducing microvascular and macrovascular complications. Symptoms of acute hyperglycemia (such as thirst, polyuria, or blurry vision) often resolve when blood glucose levels are less than 200 mg/dL. Long-term metabolic control of diabetes is best monitored by measurement of glycosylated hemoglobin ($\text{HbA}_{1\text{c}}$), which reflects glucose control over the previous 2 to 3 months. In general, $\text{HbA}_{1\text{c}}$ values less than 6.0% to 7.0% are associated with fewer microvascular complications. Compliance, age, comorbidities, and organ function (heart, kidney, liver) are all important considerations when prescribing therapy.⁵

Insulin

Because patients with type 1 diabetes mellitus do not produce insulin, they require exogenous administration of insulin therapy to survive. Insulin is prescribed for patients with type 2 diabetes mellitus if treatment with oral glucose regulators fails. In these patients, pancreatic β cells have been destroyed or autoantibodies have developed (see [Chapter 37](#) for insulin's mechanism of action). Insulin therapy mirrors the normal pattern of insulin secretion. Long-acting agents mimic basal insulin secretion and short-acting insulin administered before mealtimes to imitate pulsatile secretion in response to an increase in plasma glucose. At least two daily subcutaneous injections of intermediate- or long-acting insulin combined with rapid-acting insulin are nearly always required to achieve adequate glycemic control in type 1 diabetes.

Insulin receptors become fully saturated at low concentrations of insulin. For example, a continuous infusion of insulin at 1 to 2 units per hour has the same or even greater pharmacologic effect than a single larger intravenous (IV) dose that is cleared rapidly from the circulation. Large doses of insulin, however, will last longer and exert a greater net effect than small doses. The number of insulin receptors seems to be inversely related to the plasma concentration of insulin, which reflects the ability of insulin to regulate the population of its receptors.⁶ Obesity and type 2 diabetes mellitus appear to be associated with downregulation of important substrates in the insulin receptor pathway.⁷

Pharmacokinetics

In the basal state, insulin is secreted into the portal venous system at a rate of approximately 1 unit per hour. After food intake, the rate of insulin secretion increases 5- to 10-fold. The total daily secretion of insulin is approximately 40 units. The sympathetic and parasympathetic nervous systems innervate the insulin-producing islet cells to influence the basal rate of hormone secretion. For example, α -adrenergic stimulation decreases and β -adrenergic or parasympathetic nervous system stimulation increases the basal secretion of insulin. The insulin response to glucose is greater after oral ingestion than after IV infusion of glucose because glucose-dependent insulinotropic polypeptide is released after oral ingestion and the pancreatic β cell response is augmented.

The elimination half-time of IV insulin is 5 to 10 minutes in both healthy and diabetic patients. Insulin is metabolized in the kidneys and liver by a proteolytic enzyme. Approximately 50% of the insulin that reaches the liver through its portal vein is metabolized in a single passage. Nevertheless, renal dysfunction alters the disappearance rate of circulating insulin to a greater extent than does hepatic disease. Indeed, prolonged effects of insulin are found in patients with renal disease, reflecting impairment of both its metabolism and excretion by the kidneys. Peripheral tissues such as skeletal muscles and fat can bind and inactivate insulin, but this effect is of minor quantitative significance. Despite rapid clearance from plasma after IV injection of insulin, the pharmacologic effect lasts for 30 to 60 minutes because insulin is tightly bound to tissue receptors. Insulin administered subcutaneously releases slowly into the circulation to produce a sustained biologic effect.

Insulin Preparations and Delivery

Human insulin manufactured using recombinant DNA technology has replaced insulin extracted from beef and pork pancreas. Allergy or immunoresistance to animal insulins is no longer a serious problem. The basic principle of replacement is to provide a slow, long-acting, continuous supply of insulin (neutral protamine Hagedorn [NPH] insulin, insulin glargine, insulin detemir, or insulin degludec) that mimics the nocturnal and interprandial basal secretion of normal pancreatic β cells.⁸ A rapid and relatively short-acting form of insulin (insulin aspart, lispro, or glulisine) delivered before meals mimics the normal meal-stimulated (prandial) release of insulin.

A number of insulin preparations for subcutaneous administration are available (**Table 38.2**).⁹ The pharmacokinetics of these insulins vary from individual to individual and even within the same individual from day to day. Rates of insulin absorption from subcutaneous sites differ with the injection site (absorption from abdominal sites is least variable), depth and angle of injection, ambient temperature, and exercise of an injected extremity.

TABLE 38.2

Classification of insulin preparations

Insulin preparation	Hours after subcutaneous administration		
	Onset	Peak	Duration (hours)
Very rapid-acting			
Lispro	15-30 minutes	30-90 minutes	3-5
Insulin aspart	12-18 minutes	30-90 minutes	3-5
Glulisine	12-30 minutes	30-90 minutes	3-5
Rapid-acting			
Regular	30-60 minutes	2-4 hours	5-8
Intermediate-acting			
NPH	1-2 hours	4-12 hours	12-16
Lispro protamine	30-60 minutes	4-12 hours	12-16
Long-acting			
Detemir	1-2 hours	6-8 hours	6-24
Glargine	1-2 hours	None	20-26
Ultra long-acting			
Degludec	30-90 minutes	None	>40

Abbreviation: NPH, neutral protamine Hagedorn.

Commercially prepared insulin is bioassayed, and its physiologic activity (potency), based on the ability to decrease blood glucose concentration, is expressed in units. Insulin U-100 (100 U/mL) is the most commonly used commercial preparation. The total daily exogenous dose of insulin for treatment of type 1 diabetes mellitus is usually in the range of 0.5 to 1 U/kg per day. This insulin requirement, however, may be increased dramatically by stress associated with sepsis or trauma.

Continuous subcutaneous insulin infusion through an external pump delivers basal insulin (0.01-0.015 U/kg per hour) and bolus doses before meals. With this system, nocturnal versus daytime basal requirements can be accommodated, infusions can be altered during exercise, and doses can be calculated via algorithms of previous glucose values and insulin delivery. Short-acting insulin (regular) and ultra-rapid-acting insulins (lispro, aspart, and glulisine) are the only preparations used for continuous subcutaneous insulin infusion delivery pumps.

Lispro

Lispro is a short-acting insulin analogue that more closely parallels physiologic insulin secretion and needs. A feature of natural or synthetic human insulin is that six molecules associate with a zinc molecule to form hexamers. Insulin hexamers must dissociate to monomers before absorption from subcutaneous injection

sites. This feature is the reason that crystalline zinc insulin (regular insulin) has a peak action 2 to 4 hours after its subcutaneous injection. It must be administered 30 to 60 minutes before eating to effectively limit postprandial hyperglycemia. Lispro insulin is created by exchanging lysine and proline at positions 28 and 29 of the insulin B chain. As a result of this, hexamer formation is prevented, and the monomer is rapidly absorbed from the injection site. Therefore, lispro insulin injected subcutaneously begins to act within 15 minutes, the peak effect is reached in 30 to 90 minutes, and the duration of action is only 3 to 5 hours. Lispro injected just before eating provides a postprandial plasma insulin concentration profile like that of normal insulin secretion. An important benefit of lispro is a decrease in postprandial hyperglycemia and less risk of hypoglycemia, which may follow injection of regular insulin. Loss of the late action of regular insulin, however, may result in recurrent hyperglycemia before the next meal. In patients treated with lispro, HbA_{1c} may not decrease unless the doses of basal insulin (NPH, detemir, or glargine) are increased to better control between-meal hyperglycemia.

Insulin Aspart and Glulisine

Insulin aspart and glulisine are synthetic rapid-acting analogues with a profile of action and therapeutic benefits similar to those of lispro.

Regular Insulin (Crystalline Zinc Insulin)

Regular insulin is a fast-acting preparation and is the only form of insulin that can be administered IV as well as subcutaneously. This form can be mixed in the same syringe with other insulin preparations if the pH of the solutions is similar.

Administration of regular insulin is preferred for treating the abrupt onset of hyperglycemia or the appearance of ketoacidosis. In the perioperative period, regular insulin is administered as a single IV injection (1-5 units) or as a continuous infusion (0.5-2.0 units per hour) to treat metabolic derangements associated with diabetes mellitus.

Neutral Protamine Hagedorn

The NPH is an intermediate-acting preparation whose absorption from its subcutaneous injection site is delayed because the insulin is conjugated with protamine. The acronym NPH designates a neutral solution (N), protamine (P), and origin in Hagedorn's (H) laboratory.¹⁰ This insulin preparation contains 0.005 mg protamine per unit of insulin.

Glargine, Detemir, and Degludec

Glargine, detemir, and degludec are long-acting insulin analogues for basal insulin replacement. Compared to NPH insulin, these long-acting insulins have a later onset of action and less pronounced peaks. Glargin or detemir can be administered as a single bedtime injection to provide basal insulin for 24 hours with less nocturnal hypoglycemia.¹¹ Unlike glargin and detemir, degludec can be mixed with rapid-acting insulins. Degludec is not approved for use in the United States.

Side Effects

Side effects of treatment with insulin include (1) hypoglycemia, (2) allergic reactions, (3) lipodystrophy, (4) insulin resistance, or (5) drug interactions.

Hypoglycemia

The most serious side effect of insulin therapy is hypoglycemia. Patients are vulnerable to hypoglycemia if they receive exogenous insulin in the absence of carbohydrate intake, such as the perioperative fasting period before surgery. The first symptoms of hypoglycemia (diaphoresis, tachycardia, and hypertension) are from increased epinephrine secretion to raise the blood glucose concentration. Rebound hyperglycemia caused by sympathetic nervous system activity in response to hypoglycemia (Somogyi effect) may mask the correct diagnosis. Symptoms of hypoglycemia involving the central nervous system (CNS) include mental confusion progressing to seizures and coma. The CNS effects are intense because the brain depends on glucose as a

selective substrate for oxidative metabolism. A prolonged period of hypoglycemia may result in irreversible brain damage.

The diagnosis of hypoglycemia during general anesthesia is difficult because anesthetic drugs mask the classic signs of sympathetic nervous system stimulation. Hypoglycemia may cause changes in heart rate and systemic blood pressure.¹² The signs of sympathetic nervous system stimulation are likely to be confused with responses evoked by painful surgical stimulation in an anesthetized patient. The anesthesiologist may then decide to increase the dose of anesthetic drugs. Nonselective β-adrenergic antagonists also may mask the symptoms of hypoglycemia.

Severe hypoglycemia is treated with 50 to 100 mL of 50% glucose solution administered IV. Alternatively, glucagon, 0.5 to 1.0 mg administered IV or subcutaneously, is given. Nausea and vomiting are frequent side effects of glucagon treatment. In the absence of CNS depression, carbohydrates may be administered orally.

Allergic Reactions

Use of human insulin preparations has eliminated the problem of systemic allergic reactions that could result from administration of animal-derived insulins. Reactions to insulin preparations can be from either noninsulin components or the insulin itself. Insulin analogues, such as insulin lispro or aspart, are observed to be less allergenic, although still have the potential to cause allergic reactions. Type I hypersensitivity reactions are the most frequent and can range from local injection site swelling and erythema to less common systemic reactions, such as urticaria. Although rare, anaphylactic reactions are possible.¹³ Chronic exposure to low doses of protamine in NPH insulin may stimulate the production of antibodies against protamine. Patients may remain asymptomatic until a large dose of protamine is administered IV to antagonize the anticoagulant effects of heparin. Although patients who are treated with NPH insulin have had allergic reactions to protamine, allergic reactions to protamine are not more common in diabetic patients treated with NPH insulin than in nondiabetics.^{14,15}

Lipodystrophy

Lipodystrophy results when fat atrophies at the site of subcutaneous injection of insulin. This side effect is minimized by frequently changing the site used for injection of insulin.

Insulin Resistance

Given that insulin requirements for pancreatectomized adults are often as low as 30 units per day, diabetic patients requiring greater than 100 units of exogenous insulin per day are in a state of insulin resistance. The use of human insulins has eliminated the problem of immunoinsensitivity that could accompany administration of animal insulins. Acute insulin resistance can be seen in stress situations, such as infection or trauma, when an excess of counterregulatory hormones such as cortisol and catecholamines predominates.

Drug Interactions

Certain hormones that are administered as drugs may counter the hypoglycemic effect of insulin, including adrenocorticotropic hormone, estrogens, and glucagon. Epinephrine inhibits the secretion of insulin and stimulates glycogenolysis. Certain antibiotics (tetracycline or chloramphenicol), salicylates, and phenylbutazone increase the duration of action of insulin and may have a direct hypoglycemic effect. The hypoglycemic effect of insulin may be potentiated by monoamine oxidase inhibitors.

Other Glucose Regulators

Oral drugs with different mechanisms of action are available for controlling plasma glucose concentrations in patients with type 2 diabetes mellitus ([Table 38.3](#)). None of these drugs will adequately control hyperglycemia indefinitely. Therefore, use of combinations of oral drugs from the onset of treatment may be indicated.¹⁶ Insulin itself may be administered with oral glucose regulators. The effect on HbA_{1c} is similar for these drugs.

TABLE 38.3**Oral drugs for treatment of type 2 diabetes mellitus****Sulfonylureas (stimulate insulin secretion; hypoglycemia a risk)**

Glyburide

Glipizide

Glimepiride

Gliclazide

Tolbutamide

Tolazamide

Chlorpropamide

Acetohexamide

Biguanides (inhibit glucose production by the liver; hypoglycemia not a risk)

Metformin

Thiazolidinediones (increase sensitivity to insulin for glucose uptake by skeletal muscles and adipose tissues; hypoglycemia not a risk)

Rosiglitazone

Pioglitazone

Sodium-glucose cotransporter 2 inhibitors (increase renal glucose excretion; hypoglycemia not a risk)

Canagliflozin

Dapagliflozin

Empagliflozin

Ertugliflozin

Dipeptidyl-peptidase-4 inhibitors (increase insulin secretion; hypoglycemia not a risk)

Sitagliptin

Saxagliptin

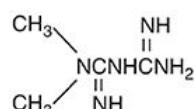
Vildagliptin

Linagliptin

Alogliptin

Metformin

Metformin is an oral biguanide that is often prescribed as the initial agent to prevent hyperglycemia in patients with type 2 diabetes ([Figure 38.1](#)). Metformin decreases blood glucose concentrations in both the fasting and postprandial state and rarely causes hypoglycemia. It can be used in combination with other medications such as insulin and sulfonylureas. Metformin should not be prescribed for patients with lactic acidosis, acute kidney injury, gastrointestinal intolerance, or acute hepatic disease. In addition to lowering blood glucose levels, metformin improves lipid profiles and fibrinolysis and promotes mild to moderate weight loss.¹⁷ Metformin also has been used in patients with polycystic ovarian disease, nonalcoholic fatty liver disease, and premature puberty.

**FIGURE 38.1** Metformin.**Pharmacokinetics**

In contrast to sulfonylureas, metformin is not bound to plasma proteins and does not undergo metabolism. It is eliminated by the kidneys, with 90% of an oral dose excreted in approximately 12 hours. Peak plasma concentrations of metformin occur approximately 2 hours after oral administration. The drug has an elimination half-time of 2 to 4 hours, which means that it is taken up to three times a day (500-1,000 mg with meals). In view of its dependence on renal clearance, metformin is prescribed with caution, if at all, to patients with renal dysfunction.

Mechanism of Action

The blood glucose-lowering effect of metformin is not mediated through stimulation of endogenous insulin secretion.¹⁸ Metformin suppresses hepatic glucose production by decreasing gluconeogenesis and glycogenolysis and enhances postprandial insulin suppression of hepatic glucose production. Metformin also regulates glucose levels by decreasing gastrointestinal glucose absorption, increasing insulin sensitivity in peripheral tissues, and enhancing synthesis of glucagon-like peptide-1 (GLP-1) in the ileum, to stimulate insulin release from pancreatic β cells.¹⁷

Side Effects

The most common side effects of metformin are anorexia, nausea, and diarrhea, which are dose related. Up to 15% of patients experience side effects sufficient to warrant withdrawal of the drug.⁵ In contrast to sulfonylureas, metformin does not cause hypoglycemia. Metformin is associated with vitamin B₁₂ deficiency.⁵ The most serious, although rare, side effect of metformin therapy is lactic acidosis.

Lactic Acidosis

Lactic acidosis is a possible side effect associated with metformin that has been described during the intraoperative period.¹⁸⁻²⁰ For this reason, some have recommended discontinuing metformin 48 hours or longer before elective operations.¹⁹ If metformin cannot be discontinued before surgery, the patient is monitored for the development of lactic acidosis (arterial blood gases and pH, serum lactate concentrations, renal function) in the perioperative period.

Metformin inhibits the mitochondrial enzyme glycerophosphate dehydrogenase to suppress glucogenogenesis in hepatocytes, which results in a decrease in the conversion of lactate to pyruvate.²¹ In patient with normal hepatic function, lactate is usually metabolized quickly in the liver. For this reason, metformin should be administered with caution, if at all, to patients with a history of hepatic dysfunction, renal insufficiency (creatinine level >1.5 mg/dL), acute myocardial infarction, congestive heart failure, arterial hypoxemia, or sepsis. For patients in need of an imaging study that requires IV administration of radiographic iodinated contrast media, metformin may be continued only if the patient has normal renal function and no evidence of acute kidney injury.²² Hemodialysis along with bicarbonate administration can be effective therapy for metformin-induced lactic acidosis. Management of biguanide-induced lactic acidosis is supportive because the underlying pathologic change (blockade of the mitochondrial respiratory chain) cannot be treated.

Sulfonylureas

Sulfonylurea compounds are drugs capable of lowering blood glucose concentrations even to hypoglycemic levels (**Figure 38.2**).^{18,23} Successful management of glucose control with sulfonylureas requires some β cell function, and its use is ineffective in the treatment of patients with type 1 diabetes mellitus. As many as 20% of patients with type 2 diabetes mellitus who begin sulfonylurea therapy do not have an adequate hypoglycemic response to maximal doses (*primary failures*), and each year, an additional 5% to 10% of patients who responded initially fail to respond to sulfonylurea therapy (*secondary failure*).^{23,24} Although sulfonylureas are derivatives of sulfonamides, they have no antibacterial actions. These drugs should not be administered to patients with known allergy to sulfa drugs.

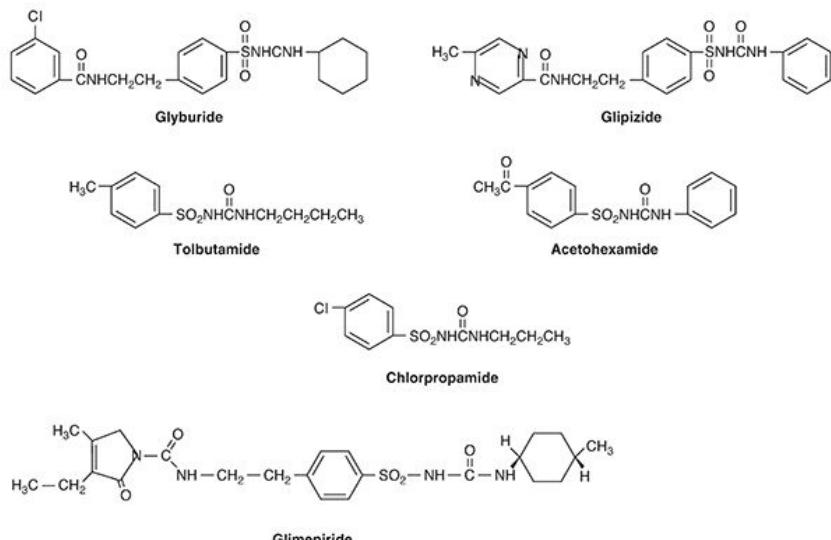


FIGURE 38.2 Oral hypoglycemics derived from sulfonylurea.

Mechanism of Action

Sulfonylurea receptors are found on pancreatic and cardiac cells. These drugs inhibit adenosine triphosphate-sensitive potassium ion channels (now known as the **sulfonylurea receptor-1**) on pancreatic β cells.⁵ As a result, there is an influx of calcium and stimulation of exocytosis (release) of insulin storage granules. Although sulfonylureas decrease insulin resistance, this effect is minor, if at all, in decreasing blood glucose concentrations.

Pharmacokinetics

Sulfonylureas are readily absorbed from the gastrointestinal tract, with the most important distinguishing features being differences in duration of action and elimination half-time (Table 38.4).²³ The biologic effects of sulfonylureas such as glyburide may be longer than plasma half-lives because of the formation of active metabolites.²⁵ Weakly acidic, sulfonylureas circulate bound to protein (90%–98%), principally to albumin. Metabolism in the liver is extensive, and the active and inactive metabolites are eliminated by renal tubular secretion. Approximately 50% of glyburide is excreted in feces.

TABLE 38.4

Classification and pharmacokinetics of sulfonylurea oral hypoglycemics

	Equivalent daily dose (mg)	Daily dose range (mg)	Doses per day	Duration of action (hours)	Elimination half-time (hours) ^a
Glyburide	2.5-5	2.5-20	1-2	18-24	4.6-12
Glipizide	5-10	5-40	1-2	12-24	4-7
Glimepiride	2	2-4	1	24+	5-8

^aApproximate.

Side Effects

Sulfonylureas are generally well tolerated; the most common severe complication of these drugs is hypoglycemia. The greatest risk of hypoglycemia occurs with drugs with the longest elimination half-times, specifically glyburide and chlorpropamide. Although hypoglycemia from sulfonylureas may be infrequent, it is often more prolonged and more dangerous than hypoglycemia from insulin (Table 38.5).

TABLE 38.5**Comparison of sulfonylurea therapy with insulin therapy**

Sulfonylurea	Insulin
Failed initial response in 10%-15% of patients	No maximum dose
Secondary failure rate each year among treated patients is about 10%.	
Hypoglycemia may be more severe.	Hypoglycemia may be more frequent.
Associated cardiac complications	Lipid levels lowered
Patients may prefer oral medication.	Patients may resist injections.

Hypoglycemia caused by sulfonylureas is treated with prolonged infusion of glucose-containing solutions. Risk factors for sulfonylurea-induced hypoglycemia include (1) impaired nutrition, as in the perioperative period; (2) age older than 60 years; (3) impaired renal function; and (4) concomitant drug therapy that potentiates sulfonylureas (phenylbutazone, sulfonamide antibiotics, warfarin) or itself produces hypoglycemia (alcohol or salicylates). Renal disease decreases elimination of sulfonylureas and their active metabolites, thus increasing the likelihood of hypoglycemia. Sulfonylurea metabolites are renally cleared, thus rendering those with short-half lives and relatively inactive metabolites (such as glipizide or glimepiride) preferable to others with longer durations of action and active metabolites (such as glyburide) for use in patients with renal insufficiency.²⁶ Sulfonylureas cross the placenta and may produce fetal hypoglycemia.

Sulfonylureas close adenosine triphosphate–sensitive potassium channels and inhibit ischemic preconditioning, a cardioprotective mechanism.²⁷ Cardiovascular mortality has been associated with some older sulfonylureas (such as tolbutamide or chlorpropamide), especially in patients who have had a prior myocardial infarction.^{28,29} Newer sulfonylureas that are selective for pancreatic β cells, such as glimepiride and gliclazide, may not be associated with the same cardiac morbidity.^{30,31} For this reason, sulfonylureas may be discontinued 24 to 48 hours before elective surgery in high-risk patients.

Approximately 1% to 3% of patients treated with sulfonylureas experience gastrointestinal disturbances including nausea, vomiting, abnormal liver function tests, and cholestasis. Sulfonylureas are not recommended for patients with hepatic dysfunction as liver disease prolongs their elimination half-time and enhances their hypoglycemic action, except for acetohexamide. Disulfiram-like reactions and inappropriate secretion of arginine vasopressin hormone that results in hyponatremia are unique side effects of chlorpropamide.

Glyburide

Glyburide stimulates insulin secretion over a 24-hour period after a morning oral dose.³² Peak plasma levels occur approximately 3 hours after an oral dose. Glyburide increases sensitivity to insulin and inhibits the production of glucose by the liver. Metabolism is in the liver, with metabolites excreted equally in urine and feces. One of the hepatic metabolites of glyburide has approximately 15% of the activity of the parent compound. A mild diuretic effect accompanies use of this drug. When administration is discontinued, the drug is cleared from plasma in about 36 hours.

Glipizide

Glipizide stimulates insulin secretion over a 12-hour period after a morning oral dose. Peak plasma levels occur approximately 1 hour after oral administration. Glipizide increases glucose uptake and suppresses glucose output by the liver.³³ These effects persist for prolonged periods (at least 3 years) without evidence of tolerance. Unlike glyburide, metabolism of glipizide in the liver produces inactive substances that are excreted in urine. A mild diuretic effect accompanies use of this drug. Relatively rapid clearance from the plasma minimizes the potential for long-lasting hypoglycemia.

Glimepiride

Glimepiride decreases blood glucose concentrations by stimulating release of insulin from the pancreas and may decrease hepatic glucose production.

Thiazolidinediones

Thiazolidinediones (TZDs), such as rosiglitazone and pioglitazone, act principally at skeletal muscle, liver, and adipose tissue via peroxisome proliferator activator receptors to decrease insulin resistance and hepatic glucose production and to increase use of glucose by the liver.³⁵ As monotherapy, these drugs decrease HbA_{1c} 1% to 1.5%. The clinical effect takes 4 to 12 weeks. The TZDs tend to decrease plasma concentrations of triglycerides and increase high-density lipoprotein and low-density lipoprotein cholesterol levels. The TZDs can cause weight gain, from an increase in extracellular fluid. The accumulation of extracellular fluid as edema is undesirable in patients with congestive heart failure. Although rosiglitazone has been associated with cardiovascular risk, particularly heart failure, this risk may be similar to the cardiovascular risks observed with other standard diabetes medications.³⁴ These drugs also are contraindicated in patients with liver failure. The possibility of drug-induced liver dysfunction is the reason that plasma concentrations of hepatic transaminases must be measured periodically.

Glucagon-like Peptide-1 Receptor Agonists

The GLP-1 receptor agonists are injectable agents that bind to receptors in the pancreas, gastrointestinal tract, and brain. These drugs exert a multitude of effects, including increasing insulin secretion from β cells, decreasing glucagon production from α cells, slowing gastric emptying, and reducing appetite, and are associated with weight loss. The GLP-1 receptor antagonists are associated with reductions in adverse cardiovascular outcomes (such as stroke or acute coronary syndrome), particularly in patients with preexisting cardiovascular disease. Not all GLP-1 receptor antagonists are known to confer such benefits; the current evidence suggests liraglutide and semaglutide are associated with improvement in cardiovascular outcomes.^{35,36} Recent consensus guidelines promote the use of such GLP-1 receptor antagonists in patients with type 2 diabetes failing to achieve adequate reduction in hyperglycemia with metformin, particularly if they have atherosclerotic cardiovascular disease.³⁷

Side Effects

Nausea, vomiting, and diarrhea are associated with GLP-1 receptor agonists. The GLP-1 receptor agonists do not cause hypoglycemia unless combined with other medications that are known to cause hypoglycemia, such as sulfonylureas and insulin.

Pharmacokinetics

The GLP-1 receptor agonists vary in their duration of action. Short-acting GLP-1 receptor agonists are more effective at lowering postprandial glucose levels, whereas long-acting agents have a greater effect on fasting glucose levels. Short-acting GLP-1 receptor agonists include lixisenatide (administered once daily) and the short-acting formulation of exenatide (administered twice daily). They are excreted in the urine and are not recommended for use in patients with renal failure.

Long-acting GLP-1 receptor agonists range from dosing once daily (liraglutide) to once weekly (dulaglutide, semaglutide, and the extended-release formulation of exenatide). Semaglutide also exists in an oral formulation, but it must be taken once daily. The longer acting GLP-1 receptor agonists undergo systemic proteolysis. Data is limited on GLP-1 receptor agonists' safety in patients with renal impairment, but current evidence does not suggest a contraindication to their use in patients with kidney disease.³⁸

Sodium-Glucose Cotransporter 2 Inhibitors

The sodium-glucose cotransporter type 2 (SGLT2) is a transport protein present in the proximal tubule and responsible for approximately 90% of glucose reabsorption in the kidneys.³⁹ The SGLT2 inhibitors, also known as gliflozins, are orally administered and rely on normal renal function to effectively lower serum glucose levels via increasing glucose excretion in the kidneys. The gliflozins are also associated with weight loss and a reduction in blood pressure. Data suggests that SGLT2 inhibitors are associated with a reduction in risk of cardiovascular events (such as stroke and myocardial infarction) and heart failure in patients with

established cardiovascular disease.^{40,41} The best evidence for such risk reduction exists for empagliflozin and canagliflozin.

Side Effects

Given that SGLT2 inhibitors lower serum glucose levels by incurring an osmotic diuresis, the resultant volume loss may cause hypotension or acute kidney injury, particularly in patients concurrently taking diuretics, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers. Thus, assessment of renal function should be conducted prior to initiation of and at regular intervals while taking SGLT2 inhibitors. Use of SGLT2 inhibitors is associated with increased risk of urinary tract and genital infections.⁴² The SGLT2 inhibitors may also reduce bone mineral density and increase the risk of fracture.

Dipeptidyl-Peptidase-4 Inhibitors

Dipeptidyl-peptidase-4 (DPP-4) is an enzyme that degrades incretin hormones (hormones that are released after eating and have glucose-lowering properties), such as GLP-1. Similar to GLP-1 receptor agonists, DPP-4 inhibitors (including saxagliptin, sitagliptin, linagliptin, alogliptin, and vildagliptin) increase insulin secretion from β cells (glucose dependent) and reduce pancreatic α cell secretion of glucagon.⁵ As opposed to SGLT2 inhibitors and GLP-1 receptor agonists, DPP-4 inhibitors have not demonstrated a reduction in cardiovascular events, and variable evidence exists for an increased risk of heart failure associated with saxagliptin.³⁷ This class of drugs is orally administered and has a duration of action of 12 to 24 hours. Dose reductions are required for patients with renal insufficiency, with the exception of linagliptin, which is primarily cleared via the enterohepatic system. However, dose adjustments are made solely because less medication is needed to reach therapeutic levels, not because of any known adverse effects of accumulation of the drug.⁴³ The DPP-4 inhibitors are overall well tolerated. Reported side effects that may be associated with DPP-4 inhibitors include musculoskeletal pain and pancreatitis.^{44,45}

Other Medications

A myriad of other medications that lower blood glucose exist but are not commonly in use in the treatment of diabetes. Meglitinides exert effects on β cells similar to sulfonylurea drugs and are associated with hypoglycemia. Acarbose and miglitol are α -glucosidase inhibitors that decrease carbohydrate digestion and absorption of disaccharides by interfering with intestinal glucosidase activity.²³ As a result, both drugs release glucose from food and are slowly absorbed from the gastrointestinal tract. Flatulence, abdominal cramping, and diarrhea are side effects that frequently result from undigested carbohydrates that reach bacteria in the lower colon. Pramlintide is an injectable medication that mimics the effects of the hormone amylin, which is secreted from pancreatic β cells and suppresses gastric emptying, increases satiety, and inhibits glucagon release. Side effects include hypoglycemia and gastrointestinal upset. Colesevelam (a bile acid sequestrant) and bromocriptine mesylate (a dopamine receptor agonist) lower glucose levels and decrease HbA_{1c} values, but the mechanisms are unclear. Neither of these medications is associated with hypoglycemia and both may cause gastrointestinal intolerance.⁵

Combination Therapy

Combination therapies target two or more different causes of hyperglycemia simultaneously. For example, insulin resistance in the liver is decreased with metformin while insulin secretion is increased with sulfonylureas. Exogenous insulin also may be part of combination therapy. The primary aim of combination therapy is to decrease HbA_{1c}; reductions in the daily insulin dose are a secondary benefit.

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Drugs for the Treatment of Hypothyroidism and Hyperthyroidism

Dasun Peramunage • Vivek K. Moitra

Hypothyroidism

Hypothyroidism is defined as a deficiency in thyroid hormone and presents with signs and symptoms outlined in **Table 39.1**. Diagnostic evaluation of hypothyroidism involves measuring serum thyroid-stimulating hormone (TSH) and serum free and total thyroxine (T_4)/triiodothyronine (T_3) (**Table 39.2**). The primary treatment of hypothyroidism is hormone replacement therapy. In primary hypothyroidism, TSH concentrations can be used to monitor this treatment. Free T_4 is an insensitive indicator and may be within the normal range when TSH is inhibited. However, measurement of free T_4 is warranted in secondary hypothyroidism when TSH release is impaired. The goals of therapy include correction of hypothyroidism to a euthyroid state (reduction of symptoms and normalization of TSH secretion), reduction in goiter size, and/or prevention of thyroid cancer recurrence.

TABLE 39.1

Signs and symptoms associated with hyperthyroidism and hypothyroidism

	Hyperthyroidism	Hypothyroidism
Constitutional	Weight loss, despite gain in appetite; heat intolerance; fatigue	Weight gain, cold intolerance, fatigue, hypothermia; myxedema
Cardiovascular	Palpitations; tachycardia; atrial fibrillation	Bradycardia; hypertension; diastolic dysfunction; pericardial effusion
Neuromuscular	Tremors; hyperreflexia	Hoarseness; neuropathy; hyporeflexia
CNS/psychiatric	Anxiety; poor concentration; insomnia	Cognitive impairment; myxedema coma; dysthymia/depression
Pulmonary	Dyspnea; tachypnea	
Gastrointestinal	Diarrhea; nausea/vomiting	Constipation
Dermatologic	Hyperhidrosis	Alopecia; dry skin
Reproductive	Disruption in menstruation	infertility
Ocular	Diplopia; proptosis; chemosis; ophthalmoplegia	
Renal/electrolytes		Hyponatremia; decreased GFR
Hematologic		Macrocytic anemia

Abbreviations: CNS, central nervous system; GFR, glomerular filtration rate.

TABLE 39.2

Laboratory assessment of thyroid function

Laboratory test	Clinical considerations
TSH	<ul style="list-style-type: none">Biotin will falsely reduce TSH measurements.
Total T_4/T_3	<ul style="list-style-type: none">Measures total bound and unbound serum T_4/T_3 hormone
Free T_4/T_3	<ul style="list-style-type: none">Heparin will falsely increase free T_4 measurements.Accuracy of free hormone assays is questionable in pregnancy and acute illness where changes in binding protein (albumin and thyroglobulin) occur.

Abbreviations: T_3 , triiodothyronine; T_4 , thyroxine; TSH, thyroid-stimulating hormone.

Synthetic Thyroxine (Levothyroxine)

Synthetic T₄ is the treatment of choice for primary hypothyroidism. In the peripheral tissues, T₄ is deiodinated to form T₃ (the active form of thyroid hormone) ([Figure 39.1](#)). In young healthy patients, initial doses range from 50 to 200 µg per day. Although formulations of T₄ (Synthroid, Levoxyl, generic preparations) may have minor differences in bioavailability, one study suggests that bioequivalence among formulations may be equivalent.^{1,2} Doses may be decreased in older patients and in patients with coronary artery disease and increased by up to 30% during pregnancy.^{3–5} The TSH levels are measured approximately 4 to 12 weeks after initiation of therapy and then every 6 months until a steady dose is established; after achieving steady state, TSH levels can be monitored yearly. Because T₄ has a half-life of 7 to 10 days, hypothyroid patients can miss several days of T₄ without adverse consequences. If the patient is unable to eat for more than a week, parenteral T₄ (80% of the patient's oral dose) can be administered.

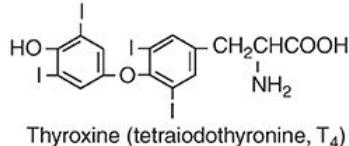
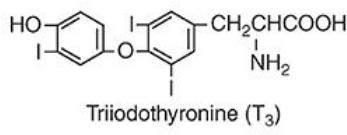


FIGURE 39.1 Thyroid gland hormones.

Triiodothyronine Formulations (Liothyronine)

Liothyronine is the levorotatory isomer of T₃ and is 2.5 to 3.0 times more potent than levothyroxine. Its rapid onset and short duration of action preclude the use of liothyronine for long-term thyroid replacement. A T₄-T₃ combination therapy may improve symptoms in a small subgroup of patients with a polymorphism in type 2 deiodinase, which converts T₄ to T₃.⁶ Both the European Thyroid Association and American Thyroid Association guidelines recommend against the routine use of combination therapy to treat hypothyroidism because outcomes with combination therapy are not significantly improved compared to monotherapy with levothyroxine.⁵

Hyperthyroidism

Excessive thyroid hormone synthesis and secretion underlie the pathophysiology of hyperthyroidism and can present clinically with signs and symptoms outlined in [Table 39.2](#). The treatments for hyperthyroidism are antithyroid drugs, radioiodine, and/or surgery. The TSH levels are useful for the diagnosis of hyperthyroidism but not for determining its degree of severity. Therefore, measuring free T₃ and T₄ is necessary to assess the efficacy of treatment. Once steady state is achieved, TSH can be used to assess the efficacy of therapy.

A large number of substances interfere with the synthesis of thyroid hormones or reduce the amount of thyroid tissue. These compounds include (1) thionamides, (2) inhibitors of the iodide transport mechanism, (3) iodide, and (4) radioactive iodine. Of these compounds, only thionamides, iodide, and radioactive iodine are used to treat hyperthyroidism.

Thionamides (Methimazole, Propylthiouracil, Carbimazole)

Thionamides are antithyroid drugs that inhibit the formation of thyroid hormone by inhibiting thyroid peroxidase to prevent incorporation of iodine into tyrosine residues of thyroglobulin ([Figure 39.2](#)).

Thionamides exert immunosuppressive effects via a reduction in concentrations of antithyrotropin-receptor antibodies. In addition to blocking hormone synthesis, propylthiouracil also inhibits the peripheral deiodination of T₄ and T₃.⁵ Carbimazole is a prodrug that is metabolized into its active form, methimazole. Antithyroid drugs are useful in the treatment of hyperthyroidism before elective thyroidectomy.

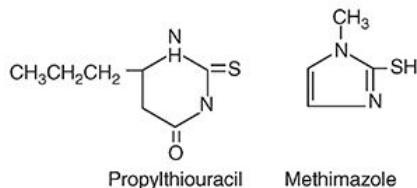


FIGURE 39.2 Antithyroid drugs.

Serum levels of thionamides peak 1 to 2 hours after ingestion.⁵ Thionamides are not available as parenteral preparations. The half-life of methimazole (4–6 h, dosed once daily) is longer than the half-life of propylthiouracil (75 min, dosed several times per day). Drug-induced decreases in excessive thyroid activity usually require several days because preformed hormone must be depleted before symptoms begin to wane. In a few patients, especially those with severe hyperthyroidism, definite improvement is evident in 1 to 2 days. Thyroid function, namely, serum T₄ and T₃ levels, is checked 4 to 6 weeks after induction of therapy and then every 2 to 3 months once the patient is euthyroid.⁸

Side Effects

Minor side effects of thionamide therapy are observed in approximately 5% of patients and include urticarial or macular skin rash, arthralgias, and gastrointestinal discomfort.⁷ Granulocytopenia and agranulocytosis are serious but rare side effects that are most likely to occur in the first 3 months of therapy with an antithyroid drug.⁷ Periodic white blood cell counts, although helpful for detecting gradual decreases in the leukocyte count, should not be relied on to detect agranulocytosis because of the rapidity with which this complication can develop. Fever or pharyngitis may be the earliest manifestation of the development of agranulocytosis. Recovery is likely if the antithyroid drug is discontinued at the first sign of this side effect. Hepatic toxicity has been reported with thionamide use, particularly propylthiouracil.^{9,10} Methimazole crosses the placenta and appears in breast milk. Placental passage, however, is limited for propylthiouracil, making it the preferred drug for use in the parturient.⁷

Iodine (Saturated Potassium Iodide Solutions, Potassium Iodide-Iodine [Lugol Solution])

Iodide is the oldest available therapy for hyperthyroidism, providing a paradoxical treatment that is effective for reasons that are not fully understood. The response of the patient with hyperthyroidism to iodide is acute and often discernible within 24 hours, emphasizing that release of hormone into the circulation is quickly interrupted. Indeed, the most important clinical effect of high doses of iodide is inhibition of the release of thyroid hormone. This may reflect the ability of iodide to antagonize the ability of TSH and cyclic adenosine monophosphate to stimulate hormone release.

Iodide is particularly useful in the treatment of hyperthyroidism before elective thyroidectomy. Indeed, the combination of oral potassium iodide and propranolol is a recommended approach.¹¹ The vascularity of the thyroid gland is also decreased by iodide therapy.¹² Chronic treatment with iodide, however, is often associated with a recurrence of previously suppressed excessive thyroid gland activity.¹³

Allergic reactions may accompany treatment with iodide or administration of organic preparations that contain iodide. Angioedema and laryngeal edema may become life threatening.

Radioactive Iodine

Radioiodine is commonly administered as the therapy of choice for Graves hyperthyroidism.¹⁴ Many practitioners administer radioactive iodine therapy to patients after euthyroidism is achieved via thionamides.

Among the radioactive isotopes of iodine, iodine 131 (^{131}I) is the most frequently administered. This isotope is rapidly and efficiently trapped by thyroid gland cells, and the subsequent emission of destructive β rays acts almost exclusively on these cells, with little or no damage to surrounding tissue. It is possible to completely destroy the thyroid gland with ^{131}I within 6 to 18 weeks.¹⁵ Indeed, hypothyroidism occurs in about 10% of treated patients in the first year after ^{131}I administration and increases about 2% to 3% each year thereafter. For this reason, iatrogenic hypothyroidism must be considered preoperatively in any patient who has previously been treated with ^{131}I .

Hyperthyroidism is treated with orally administered ^{131}I , with symptoms of excessive thyroid gland activity gradually abating over a period of 2 to 3 months. One-half to two-thirds of patients are cured by a single dose of isotope, and the remainder require an additional one to two doses. Patients should be monitored closely for hypothyroidism, and thyroid hormone replacement therapy with levothyroxine should be started once detected. The use of ^{131}I is contraindicated during pregnancy because the fetal thyroid gland would concentrate the isotope and for patients who are breastfeeding. Furthermore, radioiodine is contraindicated in patients with severe Graves orbitopathy because therapy can worsen orbitopathy.⁸ Most thyroid cancers except for follicular cancer accumulate little radioactive iodine. As a result, the therapeutic effectiveness of ^{131}I for treatment of thyroid cancer is limited.

Thyroid Storm

Thyroid storm is a rare presentation of thyrotoxicosis with a high mortality rate of 8% to 25% despite an incidence of about 0.2 per 100,000 person-years.⁸ The pathology of thyroid storm is not well understood, but risk factors include stressors such as surgery, pregnancy, trauma, and acute illness. The diagnosis of thyroid storm is based on clinical presentation along with evidence of hyperthyroidism. The Burch and Wartofsky scoring system (Table 39.3) can be used to assist in the diagnosis of suspected thyroid storm. Once the diagnosis of thyroid storm is determined, therapeutic goals should include the reduction of thyroid hormone synthesis and secretion; reduction of circulating thyroid hormone levels and their effects peripherally; and treating the underlying inciting factors. Thyroid hormone synthesis and secretion is regulated with the administration of inorganic iodine and antithyroid drugs, propylthiouracil being preferred over thiamazole for its effect of blocking T_4 to T_3 conversion. Cholestyramine is given to facilitate the excretion of free thyroid hormone and prevent reabsorption into the circulation. β -Blockade, glucocorticoids, and acetaminophen are used to regulate the systemic manifestations of thyroid storm. Propranolol, which can decrease T_4 to T_3 conversion, is the preferred β -blocker, and glucocorticoids are used to treat underlying adrenal insufficiency. Once treatment is initiated, improvement in thyroid function can be seen in about 24 hours, and definitive therapy with surgery or radioactive iodine should be considered once the patient becomes euthyroid.

TABLE 39.3

The Burch and Wartofsky scoring system for thyroid storm^a

Diagnostic criteria		Scoring points
Temperature (°C)	37.2-37.7	5
	37.8-38.2	10
	38.3-38.8	15
	38.9-39.4	20
	39.5-39.9	25
	>40	30
CNS effects	Mild (agitation)	10
	Moderate (delirium/psychosis)	20
	Severe (seizure/coma)	30
Gastrointestinal/hepatic dysfunction	Moderate (diarrhea)	10
	Severe (jaundice)	20

Tachycardia	99-109	5
	110-119	10
	120-129	15
	130-139	20
	>140	25
Congestive heart failure	Mild (pedal edema)	5
	Moderate (bibasilar rales)	10
	Severe (pulmonary edema)	15
Atrial fibrillation	Absent	0
	Present	10
Precipitant history	Negative	0
	Positive	10

Abbreviation: CNS, central nervous system.

^aA score >45 is suggestive of thyroid storm, a score of 25 to 44 is suggestive of impending thyroid storm, and a score <25 indicates that thyroid storm is unlikely.¹⁶

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Other Endocrine Drugs

Artem Emple • Vivek K. Moitra

Preparations that contain synthetic hormones identical to those secreted endogenously by endocrine glands may be administered as drugs. These synthetic hormones resemble the endogenous substances in structure and activity. Typically, the clinical application of these drugs is for hormone replacement to provide a physiologic effect. In certain patients, however, large doses of synthetic hormones are used to exert a pharmacologic effect. Recombinant DNA technology permits the incorporation of synthetic genes that code for the synthesis of specific human hormones by bacteria, thus permitting production of pure hormones devoid of allergic properties.

Corticosteroids

The actions of corticosteroids are classified according to the potencies of these compounds to (1) evoke distal renal tubular reabsorption of sodium in exchange for potassium ions (mineralocorticoid effect) or (2) produce an antiinflammatory response (glucocorticoid effect). Naturally occurring corticosteroids are cortisol (hydrocortisone), cortisone, corticosterone, desoxycorticosterone, and aldosterone ([Figure 40.1](#)). Several synthetic corticosteroids are available, principally for use to produce antiinflammatory effects. Although it is possible to separate mineralocorticoid and glucocorticoid effects using synthetic drugs, it has not been possible to separate the various components of glucocorticoid effects. Consequently, all synthetic corticosteroids, when used in pharmacologic doses for their inflammatory effects, also produce less desirable effects, such as suppression of the hypothalamic-pituitary-adrenal (HPA) axis, delirium, weight gain, and skeletal muscle wasting.

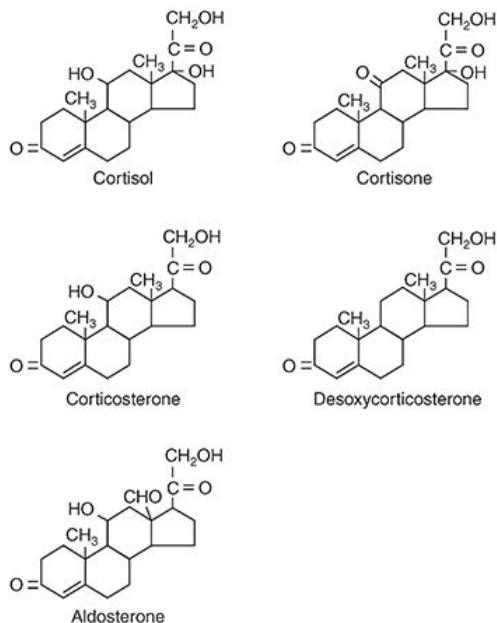


FIGURE 40.1 Endogenous corticosteroids.

Structure-Activity Relationships

All corticosteroids are constructed on the same primary molecular framework, designated as the steroid nucleus (see [Figure 40.1](#)). Changes in molecular structure may result in altered biologic responses due to

changes in absorption, protein binding, rate of metabolism, and intrinsic effectiveness of the drug at receptors. Modifications of structure, such as introduction of a double bond in prednisolone and prednisone, have resulted in synthetic corticosteroids with more potent glucocorticoid effects than the two closely related natural hormones, cortisol and cortisone, respectively (**Table 40.1**). At the same time, mineralocorticoid effects and the rate of hepatic metabolism of these synthetic drugs are less than those of the natural hormones. Despite increased antiinflammatory effects, it has not been possible to separate this response from alterations in carbohydrate and protein metabolism. This suggests that the multiple manifestations of drug-induced glucocorticoid effects are mediated by the same receptor.

TABLE 40.1

Comparative pharmacology of endogenous and synthetic corticosteroids

	Antiinflammatory potency	Sodium-retaining potency	Equivalent dose (mg)	Elimination half-time (hours)	Duration of action (hours)	Route of administration
Cortisol	1	1	20	1.5-3.0	8-12	Oral, topical, IV, IM, IA
Cortisone	0.8	0.8	25	0.5	8-36	Oral, topical, IV, IM, IA
Prednisolone	4	0.8	5	2-4	12-36	Oral, topical, IV, IM, IA
Prednisone	4	0.8	5	2-4	12-36	Oral
Methylprednisolone	5	0.5	4	2-4	12-36	Oral, topical, IV, IM, IA, epidural
Betamethasone	25	0	0.6	5	36-54	Oral, topical, IV, IM, IA
Dexamethasone	25	0	0.75	3.5-5.0	36-54	Oral, topical, IV, IM, IA
Triamcinolone	5	0	4	3.5	12-36	Oral, topical, IV, IM, epidural
Fludrocortisone	10	250	0	3.5-4.0	24	Oral, topical, IV, IM
Aldosterone	0	3,000	0	0.3	—	

Abbreviations: IA, intra-articular; IM, intramuscular; IV, intravenous.

Mechanism of Action

Glucocorticoids attach to cytoplasmic receptors to enhance or suppress changes in the transcription of DNA and thus the synthesis of proteins. Glucocorticoids also inhibit the secretion of cytokines via posttranslational effects.¹ Two distinct types of corticosteroid receptors have been identified (mineralocorticoid and glucocorticoid). Mineralocorticoid receptors are present in distal renal tubules, colon, salivary glands, and the hippocampus. In contrast, glucocorticoids receptors are more widely distributed and do not bind aldosterone, making these receptors glucocorticoid selective. Local mechanisms that result in release of steroids from their carrier proteins serve to facilitate steroid entry into cells. Target cells also contain an enzyme, 11 β -hydroxysteroid dehydrogenase that controls the interconversion of cortisol (active) and cortisone (inert). The concentration of glucocorticoid receptors may fluctuate and thus influence responsiveness to glucocorticoids.

Maintenance of Homeostasis

Permissive and protective effects of glucocorticoids are critical for the maintenance of homeostasis during severe stress. The permissive and protective actions of glucocorticoids are complementary and permit the individual to affect an appropriate stress response and to maintain homeostasis.

Permissive Actions

Permissive actions of glucocorticoids occur at low physiologic steroid concentrations and serve to prepare the individual for responding to stress. These permissive actions of glucocorticoids maintain basal activity of the HPA by providing negative feedback and by setting the threshold for a response to stress.

Protective Actions

The protective mode of glucocorticoids occurs when high plasma concentrations of steroids exert antiinflammatory and immunosuppressive effects. This protective response prevents the host-defense mechanisms that are activated during stress from overshooting and damaging the organism. Other important protective actions of glucocorticoids include redirection of metabolism to meet energy needs during stress.

Pharmacokinetics

Synthetic cortisol and its derivatives are effective orally (see [Table 40.1](#)). Antacids, but not food, interfere with the oral absorption of corticosteroids. Water-soluble cortisol succinate can be administered IV to achieve prompt increases in plasma concentrations. More prolonged effects are possible with IM injection. Cortisone acetate may be given orally or intramuscularly but cannot be administered IV. The acetate preparation is a slow-release preparation lasting 8 to 12 hours. After release, cortisone is converted to cortisol in the liver. Corticosteroids are also promptly absorbed after topical application or aerosol administration.

Cortisol is highly bound (90% or more) in the plasma to corticosteroid-binding globulin. Cortisol also binds albumin and erythrocytes.² Nevertheless, cortisol and related compounds readily cross the placenta. Small amounts of cortisol appear unchanged in the urine, but at least 70% is conjugated in the liver to inactive or poorly active metabolites. These water-soluble conjugated metabolites appear in the urine and bile. The elimination half-time of cortisol is 1.5 to 3.0 hours, but its biologic effects persist for several hours. The half-lives of synthetic glucocorticoids range from 1 hour (prednisolone) to more than 4 hours (dexamethasone), and clearance may be prolonged in older individuals.³ Individuals who clear glucocorticoids slowly may be subject to an increased incidence of side effects.⁴

Cortisol is released from the adrenal glands in an episodic manner and the frequency of pulses follows a circadian rhythm that is linked to the sleep-wake cycle. Maximal plasma concentrations of cortisol occur just before awakening and the lowest levels occur 8 to 10 hours later. Stress-induced changes in the plasma concentrations of cortisol are superimposed on the background baseline release of cortisol. Synthesis of cortisol is governed by adrenocorticotrophic hormone (ACTH) that is controlled by the hypothalamic hormones, corticotropin-releasing hormone, and arginine vasopressin (AVP).

Synthetic Corticosteroids

Synthetic corticosteroids administered for their glucocorticoid effects include prednisolone, prednisone, methylprednisolone, betamethasone, dexamethasone, and triamcinolone ([Figure 40.2](#); see [Table 40.1](#)). Fludrocortisone is a synthetic halogenated derivative of cortisol that is administered for its mineralocorticoid effect (see [Table 40.1](#) and [Figure 40.2](#)). Naturally occurring corticosteroids, such as cortisol and cortisone, are also available as synthetic drugs (see [Table 40.1](#) and [Figure 40.1](#)).

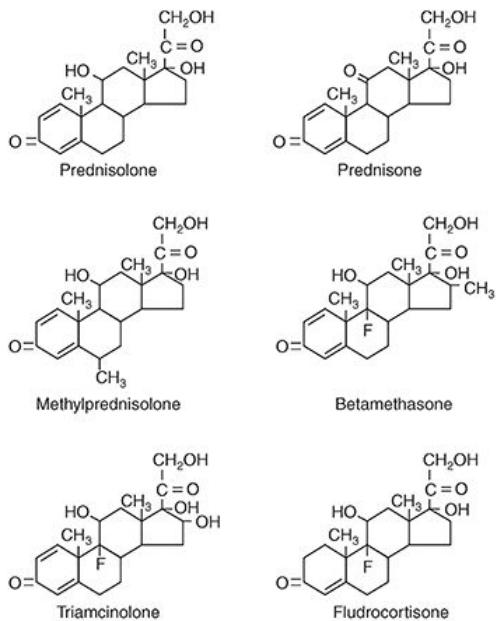


FIGURE 40.2 Synthetic corticosteroids.

Prednisolone

Prednisolone is an analogue of cortisol that is available as an oral or parenteral preparation. The antiinflammatory effect of 5 mg of prednisolone is equivalent to that of 20 mg of cortisol. This drug and prednisone are suitable for sole replacement therapy in adrenocortical insufficiency because of the presence of glucocorticoid and mineralocorticoid effects.

Prednisone

Prednisone is an analogue of cortisone that is available as an oral or a parenteral preparation. It is rapidly converted to prednisolone after its absorption from the gastrointestinal tract. Its antiinflammatory effect and clinical uses are similar to those of prednisolone.

Methylprednisolone

Methylprednisolone is the methyl derivative of prednisolone. The antiinflammatory effect of 4 mg of methylprednisolone is equivalent to that of 20 mg of cortisol. The acetate preparation administered intra-articularly has a prolonged effect. Methylprednisolone succinate is highly soluble in water and is used IV to produce an intense glucocorticoid effect.

Betamethasone

Betamethasone is a fluorinated derivative of prednisolone. The antiinflammatory effect of 0.75 mg is equivalent to that of 20 mg of cortisol. Betamethasone lacks the mineralocorticoid properties of cortisol and thus is not acceptable for sole replacement therapy in adrenocortical insufficiency. Oral or parenteral administration is acceptable.

Dexamethasone

Dexamethasone is a fluorinated derivative of prednisolone and an isomer of betamethasone. The antiinflammatory effect of 0.75 mg is equivalent to that of 20 mg of cortisol. Oral and parenteral preparations are available. The acetate preparation is used as a long-acting repository suspension. Dexamethasone sodium phosphate is water soluble, rendering it appropriate for parenteral use. This corticosteroid is commonly chosen to treat certain types of cerebral edema and prevent postoperative nausea and vomiting.

Triamcinolone

Triamcinolone is a fluorinated derivative of prednisolone. The antiinflammatory effect of 4 mg is equivalent to that of 20 mg of cortisol. Triamcinolone has less mineralocorticoid effect than does prednisolone. Oral and parenteral preparations are available. The hexacetonide preparation injected intra-articularly may provide therapeutic effects for 3 months or longer. This drug is often used for epidural injections in the treatment of lumbar disc disease.

During the first days of treatment with triamcinolone, mild diuresis with sodium loss may occur. Conversely, edema may occur in patients with decreased glomerular filtration rates. Triamcinolone does not increase urinary potassium loss except when administered in large doses.

An unusual adverse side effect of triamcinolone is an increased incidence of skeletal muscle weakness. Likewise, anorexia rather than appetite stimulation, and sedation rather than euphoria may accompany administration of triamcinolone.

Clinical Uses

The only universally accepted clinical use of corticosteroids and their synthetic derivatives is as replacement therapy for deficiency states. With this exception, the use of corticosteroids in disease states is empirical and not curative, although antiinflammatory responses exert an intense palliative effect. The safety of corticosteroids is such that it is acceptable to administer a single large dose in a life-threatening situation on the presumption that unrecognized adrenal or pituitary insufficiency may be present.

Prednisolone or prednisone is recommended when an antiinflammatory effect is desired. The low mineralocorticoid potency of these drugs limits sodium and water retention when large doses are administered to produce the desired glucocorticoid effect. It must be recognized, however, that the antiinflammatory effect of corticosteroids is palliative because the underlying cause of the response remains. Nevertheless, suppression of the inflammatory response may be lifesaving in some situations. Conversely, masking of the symptoms of inflammation may delay diagnosis of life-threatening illness, such as peritonitis due to perforation of a peptic ulcer.

Deficiency States

Acute adrenal insufficiency requires electrolyte and fluid replacement as well as supplemental corticosteroids. Cortisol is administered at a rate of 100 mg IV every 8 hours after an initial injection of 100 mg. Management of chronic adrenal insufficiency in adults is with the daily oral administration of cortisone, 25.0 to 37.5 mg. A typical regimen is 25.0 mg in the morning and 12.5 mg in the late afternoon.⁵ This schedule mimics the normal diurnal cycle of adrenal secretion. An orally effective mineralocorticoid such as fludrocortisone, 0.1 to 0.3 mg daily, is required by most patients.

Allergic Therapy

Topical corticosteroids are capable of potent antiinflammatory effects and are the mainstay of allergic therapy. These medications interfere with the inflammatory response, induce cutaneous vasoconstriction, and have antimitotic activity.⁶ Corticosteroids work by inhibiting the production of inflammatory cytokines and chemokines, thus decreasing inflammation, cellular edema, and cellular recruitment to sites of disease. Oral administration of steroids is effective but the risk of unacceptable side effects with chronic treatment limits use by this route. Side effects, although possible with topical administration of corticosteroids, are usually not significant. Unlike antihistamines that provide pharmacologic effects within 1 to 2 hours, topical corticosteroids may require 3 to 5 days of treatment to produce a therapeutic effect.

Manifestations of allergic diseases that are of limited duration, such as hay fever, contact dermatitis, drug reactions, angioneurotic edema, and anaphylaxis, can be suppressed by adequate doses of corticosteroids. Life-threatening allergic reactions, however, must be treated with epinephrine because the onset of the antiinflammatory effect produced by corticosteroids is delayed. Indeed, any beneficial effect of corticosteroids in the management of severe allergic reactions is probably related to suppression of the antiinflammatory response rather than to inhibition of production of immunoglobulins.

Asthma

Asthma is an inflammatory disease of the lungs, and inhaled glucocorticoids (beclomethasone, budesonide, fluticasone, ciclesonide, and triamcinolone) are often recommended as first-line therapy for controlling the symptoms of asthma, improving quality of life and lung function, and in preventing exacerbations.⁷ Inhaled glucocorticoids are highly lipophilic and rapidly enter airway cells, where they have direct inhibitory effects on many of the cells involved in airway inflammation. One possible antiinflammatory mechanism is the modulation of the release of cytokines from inflammatory cells. It is estimated that 80% to 90% of the dose inhaled from the metered-dose inhaler is deposited in the oropharynx and swallowed. Inhaled glucocorticoids have oropharyngeal side effects that include dysphonia and candidiasis. Dysphonia occurs in approximately one-third of treated patients and may reflect myopathy of the laryngeal muscles that is reversible when treatment is stopped. Inhaled glucocorticoids, in doses of 1,500 µg per day or less in adults and 400 µg per day or less in children, have little, if any, effect on pituitary adrenal function.

Parenteral corticosteroids are important in the emergent preoperative preparation of patients with active reactive airway disease and in the treatment of intraoperative bronchospasm. Doses equivalent to 1 to 2 mg/kg of cortisol (or the equivalent dose of prednisolone) are commonly recommended. Preoperative corticosteroid administration 1 to 2 hours before induction of anesthesia is important because the beneficial effects of corticosteroids may not be fully manifested for several hours. Corticosteroids also enhance and prolong the responses to β-adrenergic agonists. Some enhancement of β-agonist effect may be present within 1 hour, but 4 to 6 hours are required for an antiinflammatory effect. In noncompliant or newly diagnosed patients with bronchial hyperactivity, preoperative treatment with combined corticosteroids (40 mg orally for 5 days) and salbutamol (0.2 mg puffs for 5 days) but not salbutamol alone minimizes intubation-evoked bronchoconstriction.⁸

Antiemetic Effect

Dexamethasone prevents postoperative nausea and vomiting only when administered near the beginning of surgery, probably by reducing surgery-induced inflammation due to inhibition of prostaglandin synthesis.⁹ In addition, dexamethasone may exert antiemetic effects by increasing the release of endorphins resulting in mood elevation and appetite stimulation. Prophylactic administration of dexamethasone 4 mg, ondansetron 4 mg, or droperidol 1.25 mg produced similar decreases (about 26%) in the incidence of postoperative nausea and vomiting.¹⁰ Because antiemetic interventions are similarly effective and act independently, it is recommended that the safest and least expensive antiemetic should be selected for prophylaxis. Prophylaxis is rarely warranted in low-risk patients; moderate-risk patients should receive at least one intervention, and high-risk patients should receive at least two multimodal interventions.¹¹ Rescue treatments are ineffective when the same drug has already been administered for prophylaxis. A suggested treatment strategy is to administer dexamethasone in conjunction with either droperidol or ondansetron as first-line prophylaxis and to reserve the other agent as a rescue treatment.¹¹ Total intravenous anesthesia is a useful multimodal approach in those patients at high risk for postoperative nausea and vomiting. Administration of higher doses (8-10 mg) of dexamethasone are associated with reduced rates of postdischarge nausea, pain, and fatigue. This, however, must be weighed against a slightly higher rate of postoperative infection and hyperglycemia in fragile diabetic patients.¹¹ Dexamethasone is also effective in suppressing chemotherapy-induced nausea and vomiting. The elimination half-time of dexamethasone is about 3 hours, but antiemetic effects, unlike other classes of antiemetics, often persist as long as 24 hours.

Postoperative Analgesia

Glucocorticoids peripherally inhibit phospholipase enzyme that is necessary for the inflammatory chain reaction along both the cyclooxygenase and lipoxygenase pathways.¹² As a result, glucocorticoids may be effective in decreasing postoperative pain but with a different side effect profile than nonsteroidal antiinflammatory drugs. For example, administration of betamethasone 12 mg intramuscularly 30 minutes before induction of anesthesia for outpatient foot or hemorrhoid surgery, resulted in reductions in postoperative pain and the incidence of postoperative nausea and vomiting.¹³ A meta-analysis of

perioperative intravenous dexamethasone suggests that dexamethasone at doses more than 0.1 mg/kg decreases acute postoperative pain and reduces opioid use, especially when administered preoperatively.¹⁴

Cerebral Edema

Corticosteroids in large doses can reduce and prevent vasogenic cerebral edema and the resulting increases in intracranial pressure that may accompany intracranial tumors and metastatic lesions and bacterial meningitis.¹⁵ Dexamethasone, with minimal mineralocorticoid activity, is frequently selected to decrease cerebral edema and associated increases in intracranial pressure. Conversely, the administration of glucocorticoids to patients with severe head injury, cerebral infarction, and intracranial hemorrhage is not useful and can be associated with worse outcomes.^{16,17}

Aspiration Pneumonitis

The use of corticosteroids in the treatment of aspiration pneumonitis is controversial. There is evidence in animals that corticosteroids administered immediately after the inhalation of acidic gastric fluid may be effective in decreasing pulmonary damage.¹⁸ Conversely, other data show no beneficial effect or suggest that the use of corticosteroids may enhance the likelihood of gram-negative pneumonia.^{19,20} Despite the absence of confirming evidence that corticosteroids are beneficial, it is not uncommon for the treatment of aspiration pneumonitis to include the empiric use of pharmacologic doses of these drugs.

Lumbar Disc Disease

An alternative to surgical treatment of lumbar disc disease is the epidural placement of corticosteroids.²¹ Corticosteroids may decrease inflammation and edema of the nerve root that has resulted from compression. A common regimen is epidural injection of 25 to 50 mg of triamcinolone, or 40 to 80 mg of methylprednisolone, in a solution containing lidocaine at or near the interspace corresponding to the distribution of pain. Corticosteroids can be delivered to the epidural space in a variety of ways—interlaminar, transforaminal, or caudal. Advantages of an interlaminar block include ability to treat bilateral pain and need for a lower volume. Transforaminal injection carries a lower risk of inadvertent dural puncture and better ventral spread.²² In animals, the epidural injection of triamcinolone, 2 mg/kg, interferes with the ability of the adrenal cortex to release cortisol in response to hypoglycemia for 4 weeks. Injection of triamcinolone, 80 mg, into the lumbar epidural space of patients with lumbar disc disease results in acute suppression of plasma concentrations of ACTH and cortisol between 15 (midazolam sedation) and 45 minutes (midazolam not administered) of corticosteroid injection.²³ Median suppression of the HPA axis was less than 1 month, and all patients had recovered by 3 months. Exogenous corticosteroid coverage during this potentially vulnerable period should be considered in patients undergoing major stress, especially if the adrenocortical response to ACTH is subnormal. Although epidural injections of methylprednisolone may result in short-term improvement of symptoms (pain, sensory loss) due to sciatic nerve compression from a herniated nucleus pulposus, this treatment's long-term benefits such as improved functional outcomes and decreased need for surgery are less clear.^{21,24} Most studies were unable to demonstrate a change in surgical rates with epidural steroid injections. However, certain studies of surgical patients who met operative criteria have found that the use of epidural steroid injections may prevent surgery.²²

Immunosuppression

In organ transplantation, high doses of corticosteroids are often administered at the time of surgery to produce immunosuppression and decrease the risk of rejection of the newly transplanted organ. Smaller maintenance doses of corticosteroids are continued indefinitely, and the dosage is increased if rejection of the transplanted organ is threatened.

Arthritis

The criterion for initiating corticosteroid therapy in patients with rheumatoid arthritis is rapid control of symptomatic flares and progressive disability despite maximal medical therapy. Corticosteroids are

administered in the smallest dose possible that provides significant but not complete symptomatic relief. The usual initial dose is prednisolone, 10 mg or its equivalent, in divided doses. Intra-articular injection of corticosteroids is recommended for treatment of episodic manifestations of acute joint inflammation associated with osteoarthritis. However, painless destruction of the joint is a risk of this treatment.

Collagen Diseases

Manifestations of collagen diseases, such as polymyositis, polyarteritis nodosa, and Wegener granulomatosis, but not scleroderma, are decreased and longevity is improved by corticosteroid therapy. Fulminating systemic lupus erythematosus is a life-threatening illness that is aggressively treated initially with large doses of prednisone, 1 mg/kg, or its equivalent. Large doses of corticosteroids are effective for inducing a remission of sarcoidosis. In temporal arteritis, corticosteroid therapy is necessary to prevent blindness, which occurs in about 20% of untreated patients. Some forms of nephrotic syndrome respond favorably to corticosteroids. Rheumatic carditis may be suppressed by large doses of corticosteroids.

Ocular Inflammation

Corticosteroids are used to suppress ocular inflammation (uveitis and iritis) and thus preserve sight. Instillation of corticosteroids into the conjunctival sac results in therapeutic concentrations in the aqueous humor. Topical and intraocular corticosteroid therapy often increases intraocular pressure and is associated with cataractogenesis. For this reason, it is recommended that intraocular pressure be monitored when topical corticosteroids are used for more than 2 weeks. Corticosteroids are not recommended in herpes simplex infections (dendritic keratitis) of the eye. Topical corticosteroids should not be used for treatment of ocular abrasions because delayed healing and infections may occur.

Cutaneous Disorders

Topical administration of corticosteroids is frequently effective in the treatment of skin diseases. Effectiveness is increased by application of the corticosteroid as an ointment under an occlusive dressing. Systemic absorption is also occasionally enhanced to the degree that suppression of the HPA axis occurs or manifestations of Cushing syndrome appear. Corticosteroids may also be administered systemically for treatment of severe episodes of acute skin disorders and exacerbations of chronic disorders.

Postintubation Laryngeal Edema

The administration of corticosteroids is associated with a reduction in postextubation airway events and reintubation.²⁵ Prevention and treatment of postintubation laryngeal edema includes inhaled or parenteral corticosteroids, such as methylprednisolone 20-40 mg IV, or budesonide 1 mg inhaled, administered at least 4 hours before extubation. Dexamethasone, 0.6 mg/kg orally, is an effective treatment for children with mild croup.²⁶

Ulcerative Colitis

Corticosteroid therapy is indicated in selected patients with chronic ulcerative colitis. A disadvantage of this therapy is that signs and symptoms of intestinal perforation and peritonitis may be masked.

Myasthenia Gravis

Corticosteroids are usually reserved for patients with myasthenia gravis who are unresponsive to medical or surgical therapy. These drugs seem to be most effective after thymectomy. The mechanism of beneficial effects produced by corticosteroids is not known but may reflect drug-induced suppression of the production of an immunoglobulin that normally binds to the neuromuscular junction.

Respiratory Distress Syndrome

Administration of corticosteroids at least 24 hours before delivery decreases the incidence and severity of respiratory distress syndrome in neonates born between 24 and 36 weeks' gestation. Dexamethasone administered for prolonged periods (42 days) improves pulmonary and neurodevelopmental outcome of low-

birth-weight infants at risk for bronchopulmonary dysplasia.²⁷ Glucocorticoid administration in the setting of acute respiratory distress syndrome is controversial, and the effect may vary according to timing. Early administration (≤ 72 hours) of methylprednisolone in one small study has been associated with improved outcomes.²⁸ Although later administration (>14 days) of glucocorticoids is associated with an improvement in ventilator-free days, oxygenation, and lung compliance, methylprednisolone administration is also associated with increased mortality.²⁹

Leukemia

The antilymphocytic effects of glucocorticoids are used to advantage in combination chemotherapy of acute lymphocytic leukemia and lymphomas, including Hodgkin disease and multiple myeloma. For example, prednisone and vincristine produce remissions in about 90% of children with lymphoblastic leukemia.

Cardiac Arrest

Cardiac arrest is associated with lower cortisol levels (relative adrenal insufficiency), vasoplegia, and myocardial dysfunction. Recent studies preliminarily suggest that the administration of glucocorticoids (along with vasopressin and epinephrine) during a cardiac arrest may improve survival and is associated with better neurologic outcomes.³⁰ Potential explanations include attenuation of the systemic inflammatory response syndrome and enhancement of myocardial and vascular function.³¹

Septic Shock

Septic shock is associated with states of relative adrenal insufficiency, which may contribute to the vasodilated state. Corticosteroids have been shown to restore effective blood volume through increased mineralocorticoid activity and increase systemic vascular resistance due to an effect on endothelial glucocorticoid receptors.³² A meta-analysis of corticosteroid use in sepsis has reported a decrease in duration of shock, mechanical ventilation, and intensive care unit length of stay without a mortality benefit.³³ However, in 2018, the Activated Protein C and Corticosteroids for Human Septic Shock study, a randomized controlled trial of 7 days of hydrocortisone 200 mg daily with fludrocortisone 50 µg via nasogastric tube for septic shock conferred a statistically significant reduction in mortality.³⁴ A common corticosteroid regimen includes 200 to 300 mg hydrocortisone daily in divided doses for 5 to 7 days followed by a rapid taper after vasopressor withdrawal.

Side Effects

The side effects of chronic corticosteroid therapy include (1) suppression of the HPA axis, (2) electrolyte and metabolic changes, (3) osteoporosis, (4) peptic ulcer disease, (5) skeletal muscle myopathy, (6) central nervous system dysfunction, (7) peripheral blood changes, and (8) inhibition of normal growth. Increased susceptibility to bacterial or fungal infection accompanies treatment with corticosteroids. Corticosteroid administration is associated with greater clearance of salicylates and decreased effectiveness of anticoagulants. Systemic corticosteroids used for short periods of time (<7 days) even at high doses are unlikely to cause adverse side effects. Inhaled corticosteroids are unlikely to evoke adverse systemic effects.

Corticosteroid Supplementation in the Perioperative Period

Corticosteroid supplementation should be increased whenever the patient being treated for chronic hypoadrenocorticism undergoes a surgical procedure. This recommendation is based on the concern that these patients are susceptible to cardiovascular collapse because they cannot release additional endogenous cortisol in response to the stress of surgery. More controversial is the management of patients who may manifest suppression of the HPA axis because of current or previous administration of corticosteroids for treatment of a disease unrelated to pituitary or adrenal function. Recommendations that prescribe supraphysiologic doses have been advocated despite the absence of supporting scientific data.³⁵ In adrenalectomized primates undergoing general anesthesia and surgery, the animals receiving physiologic replacement doses of cortisol were indistinguishable from those receiving supraphysiologic doses (10 times the normal production rate) of

cortisol.³⁶ Subphysiologically treated animals (one-tenth the normal production rate) were hemodynamically unstable during surgery and had a significantly higher mortality rate. Based on these animal data, it was concluded that there is no advantage in supraphysiologic glucocorticoid prophylaxis during surgical stress, and replacement doses of cortisol equivalent to the daily unstressed cortisol production rate are sufficient to allow homeostatic mechanisms to function during surgery.³⁶

Patients taking greater than 20 mg per day of prednisone or its equivalent for more than 3 weeks have a suppressed HPA axis. Patients taking less than 5 mg per day of prednisone or its equivalent can be considered not to have suppression of their HPA axis. However, patients taking 5 to 20 mg per day of prednisone or its equivalent for more than 3 weeks may or may not have suppression of the HPA axis.

A rational regimen for corticosteroid supplementation in the perioperative period is to avoid steroid supplementation in patients who do not have a suppressed HPA axis (patients taking any dose of glucocorticoids for less than 3 weeks or a daily dose of prednisone <5 mg).

Patients taking 5 to 20 mg per day of prednisone or its equivalent for more than 3 weeks may or may not have suppression of the HPA axis. These patients may benefit from further assessment of their HPA axis.

Glucocorticoid supplementation considers preoperative doses and the stress of surgery.

For patients with a suppressed HPA axis (patients taking >20 mg prednisone per day for more than 3 weeks), glucocorticoid supplementation should consider the stress of surgery. For minor surgical stress (inguinal hernia repair), the daily cortisol secretion rate and static plasma cortisol measurements suggest that a glucocorticoid replacement dose of 25 mg of hydrocortisone or 5 mg of methylprednisolone is sufficient. If the postoperative course is uncomplicated, the patient can be returned the next day to the prior glucocorticoid maintenance dose. For moderate surgical stress (nonlaparoscopic cholecystectomy, colon resection, total hip replacement), cortisol production rates suggest the glucocorticoid requirement is about 50 to 75 mg daily of hydrocortisone for 1 to 2 days. For major surgical stress (pancreatoduodenectomy, esophagectomy, cardiopulmonary bypass), the glucocorticoid dose should be 100 to 150 mg of hydrocortisone daily for 2 to 3 days. Even with this coverage, vascular collapse has been described in a patient experiencing massive hemorrhage during surgery.³⁷ This approach maintains the plasma concentration of cortisol above normal during major surgery in patients receiving chronic treatment with corticosteroids and manifesting a subnormal response to the preoperative infusion of ACTH (Figure 40.3).³⁸ In those instances in which events such as burns or sepsis could exaggerate the need for exogenous corticosteroid supplementation, the continuous infusion of cortisol, 100 mg every 12 hours, should be sufficient. Indeed, endogenous cortisol production during stress introduced by major surgery or extensive burns is not greater than 150 mg daily.^{39,40} It is likely that patients undergoing minor operations will need minimal to no additional corticosteroid coverage during the perioperative period.

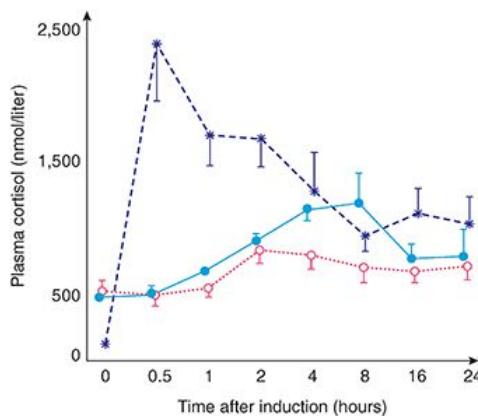


FIGURE 40.3 Administration of cortisol, 25 mg intravenously, plus a continuous infusion of 100 mg over 24 hours, maintains the plasma cortisol concentration above normal in patients (asterisk) receiving chronic treatment with corticosteroids and manifesting a subnormal response to the preoperative infusion of adrenocorticotropic hormone. Reprinted from Symreng T, Karlberg BE, Kågedal B, et al. Physiological

cortisol substitution of long-term steroid-treated patients undergoing major surgery. Br J Anesth. 1981;53(9):949-954. Copyright © 1981 Elsevier. With permission.

In addition to intravenous supplementation with cortisol, patients receiving daily maintenance doses of a corticosteroid should also receive this dose with the preoperative medication on the day of surgery. There is no objective evidence to support increasing the maintenance dose of corticosteroid preoperatively.⁴¹

Electrolyte and Metabolic Changes and Weight Gain

Hypokalemic metabolic alkalosis reflects mineralocorticoid effects of corticosteroids on distal renal tubules, leading to enhanced absorption of sodium and loss of potassium. Edema and weight gain accompany this corticosteroid effect. Corticosteroids inhibit the use of glucose in peripheral tissues and promote hepatic gluconeogenesis. The resulting corticosteroid-induced hyperglycemia can usually be managed with diet, insulin, or both. The dose requirement for oral hypoglycemic agents may be increased by corticosteroids. There is a redistribution of body fat characterized by deposition of fat in the back of the neck (buffalo hump), supraclavicular area, and face (moon facies) and loss of fat from the extremities. The mechanism by which corticosteroids elicit this redistribution of fat is not known. Peripherally, corticosteroids mobilize amino acids from tissues. This catabolic effect manifests as decreased skeletal muscle mass, osteoporosis, thinning of the skin, and a negative nitrogen balance.

Osteoporosis

Osteoporosis, vertebral compression fractures, and rib fractures are common and serious complications of corticosteroid therapy that can be found in patients of all ages. Corticosteroids appear to inhibit the activities of osteoblasts and stimulate osteoclasts by inhibition of calcium absorption from the gastrointestinal tract, which causes an increased secretion of parathyroid hormone (PTH). Osteoporosis is an indication for withdrawal of corticosteroid therapy. Evidence of osteoporosis should be sought on radiographs of the spines of patients being treated chronically with corticosteroids. The presence of osteoporosis could predispose patients to fractures during positioning in the operating room. Bisphosphonates are effective in decreasing vertebral fractures in patients taking corticosteroids.⁴²

Peptic Ulcer Disease

Although a cause-and-effect relationship has not been proved, the incidence of peptic ulcer disease seems to be increased by chronic corticosteroid therapy. Indeed, corticosteroids may decrease the normal protective barrier provided by gastric mucus.

Skeletal Muscle Myopathy

Skeletal muscle myopathy characterized by weakness of the proximal musculature is occasionally observed in patients taking large doses of corticosteroids. In some patients, this skeletal muscle weakness is so severe that ambulation is not possible and corticosteroid therapy must be discontinued.

Central Nervous System Dysfunction

Corticosteroid therapy is associated with an increased incidence of neuroses and psychoses. Behavioral changes include manic depression and suicidal tendencies. Cataracts develop in almost all patients who receive prednisone, 20 mg daily, or its equivalent for 4 years.

Peripheral Blood Changes

Corticosteroids tend to increase the hematocrit and number of circulating leukocytes. Conversely, a single dose of cortisol decreases by almost 70%—the number of circulating lymphocytes, and by more than 90%—the number of circulating monocytes in 4 to 6 hours. This acute lymphocytopenia most likely reflects sequestration from the blood rather than destruction of cells.

Inhibition of Normal Growth

Inhibition or arrest of growth can result from the administration of relatively small doses of glucocorticoids to children. The mechanism of this effect is presumed to be the generalized inhibitory effect of glucocorticoids on DNA synthesis and cell division.

Inhibitors of Corticosteroid Synthesis

Metyrapone

Metyrapone decreases cortisol synthesis by inhibition of the 11- β -hydroxylation reaction, resulting in accumulation of 11-deoxycortisol. Metyrapone may induce acute adrenal insufficiency in patients with decreased adrenocortical function. A deficiency of mineralocorticoids does not occur because metyrapone-induced inhibition of 11- β -hydroxylation results in increased production of the mineralocorticoid 11-desoxycorticosterone.

Metyrapone has been used in the diagnosis of adrenal insufficiency and treatment of excessive adrenocortical function that results from adrenal neoplasms that function autonomously or as a result of ectopic production of ACTH by tumors.

Mitotane

Mitotane, a synthetic derivative of the insecticide dichlorodiphenyltrichloroethane, has been used as adjuvant treatment for adrenocortical carcinoma as well as for nonoperative cancer. The exact mechanism has yet to be elucidated; however, it inhibits and has direct cytotoxic effects on the adrenal cortex.⁴³

Drugs That Regulate Calcium

Calcium is ingested and absorbed in the gastrointestinal tract, resorbed by bone, and filtered and reabsorbed by the kidney. The effects of PTH, calcitonin, and vitamin D metabolites regulate calcium homeostasis (see Chapter 37). The PTH regulates extracellular calcium concentration through action on the bone, kidney, and intestine. The PTH secretion is activated by hypocalcemia and elevated phosphorous levels. The net effect of PTH is to increase extracellular calcium. An excess or deficiency of calcium can disrupt coagulation, neurotransmitter and hormone secretion, neuromuscular excitability, muscle contraction, hormone action, and enzyme function.

Hypercalcemia

Hypercalcemia can be categorized as either parathyroid dependent or non-parathyroid dependent. Disorders of the parathyroid gland that result in hypercalcemia include primary and tertiary hyperparathyroidism, familial hypocalciuric hypercalcemia, and lithium-induced hypercalcemia. Hypercalcemia of malignancy is usually associated with destructive bone lesions or secretion of a PTH-like tumor peptide (PTH-related protein). Hypercalcemia from parathyroid disease is associated with bone loss and osteoporosis. Management of hypercalcemia includes intravenous fluids, bisphosphonates, calcitonin (see Chapter 37), glucocorticoids, and other less commonly used medications such as cinacalcet and denosumab.

Bisphosphonates

Bisphosphonates (pamidronate, zoledronate, alendronate, etc) are pyrophosphate analogues that lower calcium levels by inhibiting osteoclastic-mediated bone reabsorption. Hypercalcemia from malignancy, primary hyperparathyroidism, vitamin A intoxication, granulomatous disease, and Paget disease has been successfully managed with bisphosphonate therapy. Renal injury and jaw osteonecrosis has been reported in patients who take bisphosphonates. These medications should be prescribed early in the course of hypercalcemia because clinically significant reductions in calcium levels may not be observed for 2 days.

Glucocorticoids

In the setting of hypercalcemia from solid tumors and primary hyperparathyroidism, glucocorticoids are minimally effective agents. Glucocorticoids decrease synthesis of 1,25-dihydroxyvitamin D to decrease intestinal absorption of calcium and increase renal excretion of calcium.

Hypocalcemia

Preoperative patients with rhabdomyolysis, pancreatitis, sepsis, burns, fat embolism syndrome, recent massive transfusion, hypoalbuminemia, hypomagnesemia, or renal insufficiency are at risk for hypocalcemia. Chronic hypocalcemia may have few clinical signs or symptoms, whereas rapidly developing hypocalcemia may have impressive clinical effects. The most common setting for symptomatic hypocalcemia is within 12 to 24 hours after surgery, particularly after total or subtotal thyroidectomy or four-gland parathyroid exploration or removal.

Long-standing hypocalcemia with hyperphosphatemia and PTH deficiency is associated with calcification of the basal ganglia with extrapyramidal signs. Hypocalcemia can cause neuromuscular irritability, arrhythmias, congestive heart failure (decreased myocardial contractility), and hypotension. Acute, severe hypocalcemia (total serum calcium levels <7.5 mg/dL, normal albumin) is a medical emergency associated with death from laryngeal spasm or grand mal seizures. Intravenous calcium is indicated for acute symptomatic hypocalcemia. Ten percent calcium gluconate contains less elemental calcium than calcium chloride but is less likely to cause tissue necrosis during an extravasation.

Drugs for Pituitary Function

Anterior Pituitary Hormones

Anterior pituitary hormones include (1) growth hormone; (2) prolactin; (3) gonadotropins, including luteinizing hormone and follicle-stimulating hormone; (4) ACTH; and (5) thyroid-stimulating hormone. Growth hormone, gonadotropins, and ACTH can be administered in the form of synthetic drugs.

Perioperative replacement of anterior pituitary hormones may be necessary for patients receiving exogenous hormones because of a prior hypophysectomy. For example, cortisol must be provided continuously. Conversely, thyroid hormones have such a long elimination half-time that they can be omitted for several days without adverse effects. Likewise, the loss of other anterior pituitary hormones has no immediate physiologic implications.

Growth Hormone

Recombinant growth hormone is administered subcutaneously and daily to treat growth hormone deficiency. Growth hormone is also used to manage growth failure from chronic kidney disease and short stature from Turner syndrome, Prader-Willi syndrome, Noonan syndrome, and mutations in the short stature homeobox gene. Radioimmunoassays for growth hormone are used to measure plasma concentrations of the hormone. Treatment is maintained and titrated for months to years in response to growth velocity and insulin-like growth factor 1 levels (which are associated with growth velocity) and is often discontinued when linear growth decreases to less than 1 in per year.^{44,45}

Octreotide

Octreotide is a somatostatin analogue that inhibits the release of growth hormone, making it an effective treatment for patients with acromegaly.⁴⁶ Long-term treatment with octreotide (>1 month) is associated with an increased incidence of cholesterol gallstones (occurring in 20%-30% of treated patients). Because somatostatin analogues also inhibit the secretion of insulin, decreased glucose tolerance and even overt hyperglycemia might be expected during treatment with octreotide. Octreotide may be a lifesaving treatment in patients experiencing an acute carcinoid crisis although bolus injection of this somatostatin analogue may be accompanied by bradycardia and second- and third-degree heart block.⁴⁷ Octreotide is administered in acute upper gastrointestinal bleeding to decrease splanchnic blood flow and gastric acid secretion, especially prior to definitive endoscopic treatment.

Gonadotropins

Gonadotropins are used most often for the treatment of infertility and cryptorchism. Induction of ovulation can be stimulated in females who are infertile because of pituitary insufficiency. Excessive ovarian enlargement and maturation of many follicles, leading to multiple births, is a possibility. Gonadotropins are

effective only by parenteral injection. Radioimmunoassays are useful in measuring plasma and urine concentrations of gonadotropins.

Adrenocorticotrophic Hormone

The physiologic and pharmacologic effects of ACTH result from this hormone's stimulation of secretion of corticosteroids from the adrenal cortex, principally cortisol. An important clinical use of ACTH is as a diagnostic aid in patients with suspected adrenal insufficiency. For example, a normal increase in the plasma concentration of cortisol in response to the administration of ACTH rules out primary adrenocortical insufficiency. Furthermore, ACTH may be administered therapeutically to evoke the release of cortisol. Treatment of disease states with ACTH is not physiologically equivalent to administration of a specific hormone because ACTH exposes the tissues to a mixture of glucocorticoids, mineralocorticoids, and androgens. Indeed, there may be associated retention of sodium, development of hypokalemic metabolic alkalosis, and appearance of acne, which are unlikely to accompany selective-acting corticosteroids.

Absorption of ACTH after IM injection is prompt. After intravenous injection, ACTH disappears rapidly from the plasma, with an elimination half-time of about 15 minutes. Allergic reactions ranging from mild fever to life-threatening anaphylaxis may be associated with administration of ACTH.

Melatonin

Melatonin (*N*-acetyl-5-methoxytryptamine) is the principal substance secreted by the pineal gland (Figure 40.4).⁴⁸ The mammalian pineal gland is a neuroendocrine transducer. Photic information from the retina is transmitted to the pineal gland through the suprachiasmatic nucleus of the hypothalamus and the sympathetic nervous system. The neural input to the gland is norepinephrine and the output is melatonin. The synthesis and release of melatonin are stimulated by darkness and inhibited by light. As the synthesis of melatonin increases, the hormone enters the bloodstream through passive diffusion. Melatonin is rapidly metabolized, chiefly in the liver, by hydroxylation to 6-hydroxymelatonin, and, after conjugation with sulfuric or glucuronic acid, is excreted in the urine. Intravenous melatonin is rapidly distributed, and the elimination half-time is 0.5 to 5.6 minutes. The bioavailability of orally administered melatonin varies widely.

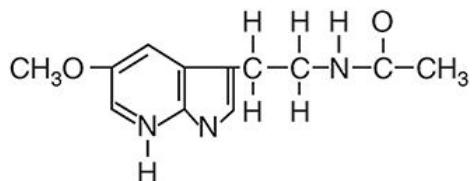


FIGURE 40.4 Melatonin.

Dose-dependent physiologic effects of melatonin include biologic regulation of circadian rhythms, sleep, mood, and perhaps reproduction, tumor growth, and aging.⁴⁸ In humans, the circadian rhythm for the release of melatonin from the pineal gland is closely synchronized with the habitual hours of sleep. Alterations in synchronization due to phase shifts (acute change in time zones or working hours) are correlated with sleep disturbances. Ingestion of melatonin affects the speed of falling asleep as well as the duration and quality of sleep and has hypnotic effects. The circadian cycle of body temperature is linked to the 24-hour cycle of subjective sleepiness and inversely related to serum melatonin concentrations. Nevertheless, sleep-promoting doses of melatonin do not have any effect on body temperature. It is unclear whether the beneficial effect of exogenous melatonin on symptoms of jet lag is due to a hypnotic effect or resynchronization of the circadian rhythm. Melatonin may improve sleep hygiene or delirium rates in the intensive care unit, but this has not been prospectively evaluated. The Prophylactic Melatonin for Delirium in Intensive Care study is a planned multicenter randomized placebo-controlled trial evaluating melatonin as a prophylactic agent to prevent delirium. The trial has completed recruitment and is in the process of data collection.⁴⁹

Posterior Pituitary Hormones

The AVP (also known as antidiuretic hormone) and oxytocin are the two principal hormones secreted by the posterior pituitary. The AVP targets the renal collecting ducts to increase permeability of cell membranes to water and promote passive water reabsorption from renal collecting ducts into extracellular fluid. The AVP also elicits intense arterial vasoconstriction via activation of vascular V₁a receptors.⁵⁰ Oxytocin elicits contractions of the uterus, which are indistinguishable from those that occur in spontaneous labor.

Arginine Vasopressin

Vasopressin is the exogenous preparation of AVP used for (1) treatment of AVP-sensitive diabetes insipidus, (2) management of refractory hypotension during anesthesia, (3) management of uncontrolled hemorrhage from esophageal varices, (4) hemodynamic stabilization in the presence of hemorrhagic and septic shock, and (5) management of refractory cardiac arrest. This drug is not effective in the management of patients with nephrogenic diabetes insipidus.

Diabetes Insipidus

Inadequate secretion of vasopressin by the posterior pituitary causes diabetes insipidus. Excessive water loss and hypernatremia via polyuria follow. Neurotrauma and surgery of the pituitary and hypothalamus, cerebral ischemia, or cerebral malignancy can cause diabetes insipidus.⁵⁰ Nephrogenic diabetes insipidus resulting from an inability of the renal tubules to respond to adequate amounts of centrally produced AVP does not respond to exogenous administration of the hormone or its congeners.

Vasopressin administered IV is used for the initial evaluation of patients with suspected diabetes insipidus, which may follow head trauma or hypophysectomy. Under these circumstances, polyuria may be transient, and a longer antidiuretic effect (1-3 days) as produced by IM vasopressin tannate in oil could produce water intoxication. Oral administration of vasopressin is followed by rapid inactivation by trypsin, which cleaves a peptide linkage. Likewise, intravenous administration of vasopressin results in a brief effect because of rapid enzymatic breakdown of peptides in the tissues, especially the kidneys.

Administration of the synthetic selective V₂ receptor agonist, desmopressin (DDAVP), treats central diabetes insipidus. The DDAVP has an intense antidiuretic (V₂) effect and decreased pressor (V₁) effect. Through its V₂ effects, DDAVP also causes endothelial cells to release von Willebrand factor, tissue-type plasminogen activator, and prostaglandins. The elimination half-time of DDAVP is 2.5 to 4.4 hours.⁵¹ There are fewer side effects produced by DDAVP than are associated with vasopressin, although nausea and increases in systemic blood pressure can occur. The DDAVP, which is not inactivated by trypsin can be administered orally (0.3-0.6 mg per day), IV (1-4 µg per day), or nasally (5-40 µg per day).⁵⁰

Administered intranasally twice daily, using a calibrated catheter (rhinyle), DDAVP is the drug of choice in the treatment of diabetes insipidus due to inadequate production of AVP by the posterior pituitary. The DDAVP, like all the AVP analogues, is not effective in the treatment of nephrogenic diabetes insipidus. Increased release of von Willebrand factor accounts for the hemostatic activity of DDAVP in patients with uremia, chronic liver disease, and certain types of hemophilia by promoting platelet adhesiveness to the vascular endothelium. The DDAVP has also been reported to minimize intraoperative blood loss in patients undergoing cardiac surgery with cardiopulmonary bypass, whereas other reports find no effect on blood loss in patients undergoing cardiac surgery or spinal fusion surgery.⁵²⁻⁵⁴ The DDAVP does not decrease bleeding following cardiopulmonary bypass in patients who were maintained on aspirin therapy until the day before surgery.⁵⁵ The DDAVP administered IV may decrease systemic vascular resistance leading to hypotension.⁵²

Lypressin is a synthetic analogue of AVP that produces antidiuresis for about 4 hours after intranasal administration. Its short duration of action limits its usefulness in the treatment of diabetes insipidus.

Hypotension During Anesthesia

Perioperative administration of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers inhibits the renin-angiotensin system and can cause refractory hypotension after administration of anesthesia.⁵⁶ In these cases, catecholamine administration may be unsuccessful.⁵⁷ The synthetic vasopressin analogue, terlipressin (1 mg), has been used to manage refractory hypotension in patients who have taken

angiotensin-converting enzyme inhibitor or angiotensin II receptor blockers.^{58,59} Vasopressin may be effective to treat hypotension from anaphylaxis and from severe catecholamine deficiency after resection of a pheochromocytoma.^{60,61}

Septic Shock

Excess generation of nitric oxide, activation of the renin-angiotensin system, and low plasma concentrations of vasopressin contribute to progressive loss of vascular tone during sepsis.⁶² Vasopressin levels are initially elevated with the onset of sepsis but decrease to normal levels after 24 hours producing a relative vasopressin deficiency.⁶³ Vasopressin infusion (0.01-0.04 unit per minute) can reverse systemic hypotension and decrease norepinephrine dosages in catecholamine-resistant septic shock.⁶⁴

Refractory Cardiac Arrest

Vasopressin, 40 units IV, was previously used as an alternative for out of hospital cardiac arrest. In the most recent American Heart Association guidelines, vasopressin was removed from the algorithm because it did not show an advantage as a substitute for epinephrine.⁶⁵ However, in the monitored setting of the operating room, clinical progression to shock and circulatory failure is often witnessed. Precipitating causes are often known and can be readily reversed. The anesthesiologist is adept at administering titrated boluses of vasopressors, and in this setting, it is likely reasonable to give vasopressin especially in the setting of right ventricular failure or pulmonary hypertensive crisis.⁶⁶ Vasopressin functions as a vasoconstrictor when it is administered in supraphysiologic doses, which serve to displace peripheral blood volume to the central circulation without some of the adverse effects produced by epinephrine. This drug needs to only be administered once during cardiopulmonary resuscitation because of its 10- to 20-minute elimination half-time. Vasopressin administered during cardiac arrest and hemorrhagic shock may improve vital organ blood flow during cardiopulmonary resuscitation and stabilize cardiocirculatory function after successful resuscitation.⁶⁷

Esophageal Varices

Vasopressin may serve as an adjunct in the control of bleeding esophageal varices and during abdominal surgery in patients with cirrhosis and portal hypertension. Infusion of 20 units over 5 minutes results in marked decreases in hepatic blood flow lasting about 30 minutes. Only a moderate increase in systemic blood pressure occurs. This effect on the portal circulation is attributable to marked splanchnic vasoconstriction. An alternative to systemic administration is the infusion of vasopressin directly into the superior mesenteric artery. It has not been established whether selective arterial administration is safer than systemic administration with respect to cardiac and vascular side effects.

Side Effects

Vasoconstriction and increased systemic blood pressure occur only with doses of vasopressin that are much larger than those administered for the treatment of diabetes insipidus. This response is because of a direct and generalized effect on vascular smooth muscles that is not antagonized by denervation or adrenergic-blocking drugs. Facial pallor due to cutaneous vasoconstriction may also accompany large doses of vasopressin. The magnitude of increase in systemic blood pressure caused by vasopressin depends, to some extent, on the reactivity of the baroreceptor reflexes. For example, when baroreceptor reflexes are depressed by anesthesia, smaller amounts of vasopressin are capable of evoking a pressor response. Vasopressin causes a relatively larger increase in systemic vascular resistance than peripheral vascular resistance, which makes it an ideal vasopressor for patients who have pulmonary hypertension. However, higher doses of vasopressin may cause splanchnic, digit, and coronary ischemia.⁶⁸

Vasopressin, even in small doses, may produce selective vasoconstriction of the coronary arteries, with decreases in coronary blood flow manifesting as angina pectoris, electrocardiographic evidence of myocardial ischemia, and, in some instances, myocardial infarction. Ventricular cardiac dysrhythmias may accompany these cardiac effects.

Large doses of vasopressin stimulate gastrointestinal smooth muscle, and the resulting increased peristalsis may manifest as abdominal pain, nausea, and vomiting. Smooth muscle of the uterus is also stimulated by large doses of vasopressin.

A decrease in platelet count has been attributed to AVP-mediated platelet aggregation via V₁ receptors.⁶⁴ The AVP infusion in advanced vasodilatory shock does not increase plasma concentrations of factor VIII, von Willebrand factor antigen, and ristocetin cofactor. Allergic reactions ranging from urticaria to anaphylaxis may occasionally follow the administration of vasopressin. Prolonged use of vasopressin may result in antibody formation and a shortened duration of action of the drug.

Oxytocin

Oxytocin stimulates uterine muscle and is administered to induce labor at term, reduce and prevent uterine atony, and decrease hemorrhage in the postpartum or postabortion period.⁶⁹ By stimulating smooth muscle uterine contraction, blood loss at the site of placental attachment is reduced. All preparations of oxytocin used clinically are synthetic, and their potency is described in units. These synthetic preparations are identical to the hormone normally released from the posterior pituitary but devoid of contamination by other polypeptide hormones and proteins found in natural proteins.

For induction of labor, a continuous infusion is preferred because the low dose of oxytocin needed can be precisely controlled. Indeed, the sensitivity of the uterus to oxytocin increases as pregnancy progresses. To induce labor, a dilute solution (10 mU/mL) is administered by a constant infusion pump beginning at 1 to 2 mU per minute. This infusion rate is increased 1 to 2 mU per minute every 15 to 30 minutes until an optimal response (uterine contraction every 2-3 minutes) is obtained. The average dose of oxytocin to induce labor is 8 to 10 mU per minute. Infusion rates up to 40 mU per minute of oxytocin may be necessary to treat uterine atony initially after delivery. The IM injections of oxytocin are commonly used to provide sustained uterine contractions in the postpartum period.

To prevent uterine atony, slow administration (to reduce adverse side effects) of 1 to 3 international unit of oxytocin over 30 seconds is recommended. Coadministration with phenylephrine may be required if higher doses are used. To manage uterine atony and postpartum hemorrhage, 3 to 5 international unit of intravenous oxytocin over 30 seconds is recommended.⁷⁰ Prior oxytocin exposure promotes oxytocin receptor downregulation and desensitization and may be a risk factor for postpartum hemorrhage from uterine atony.^{71,72}

Side Effects

High and bolus doses of oxytocin are more likely to decrease systolic and diastolic blood pressure via a direct relaxant effect on vascular smooth muscles.⁷³ Reflex tachycardia and increased cardiac output accompany the transient decrease in systemic blood pressure.⁷⁴ The amounts of oxytocin administered for most obstetric purposes are inadequate to produce marked alterations in systemic blood pressure. A marked decrease in blood pressure, however, may occur if oxytocin is administered to patients with blunted compensatory reflex responses, as may be produced by anesthesia. Likewise, hypovolemic patients may be particularly susceptible to oxytocin-induced hypotension. The hemodynamic effects of a second dose of oxytocin are diminished compared to the initial dose.⁷⁵

In the past, oxytocin preparations were often contaminated with ergot alkaloids, resulting in exaggerated systemic blood pressure increases when administered to patients previously treated with a sympathomimetic. Modern synthetic commercial preparations are pure oxytocin and do not introduce the risk of exaggerated vasoconstriction when administered in the presence of a sympathomimetic drug.

Oxytocin exhibits a slight AVP-like activity when administered in high doses, introducing the possibility of water intoxication, hyponatremia, and neurologic dysfunction if an excessive volume of fluid is administered.⁷⁶ The risk of this complication can be minimized by infusion of oxytocin in an electrolyte-containing solution rather than glucose in water.

Drugs for Reproductive Regulation

Ovarian Hormones

An understanding of the synthesis and action of ovarian hormones, including estrogens and progesterone, permits therapeutic interventions in certain disease states. Equally important is the therapeutic use of drugs that can mimic effects of these hormones and act as contraceptives.

Estrogens

Estrogens are effective in treating unpleasant side effects of menopause (Figure 40.5). Hormone replacement therapy may reduce the depressive symptoms during menopause.⁷⁷ Senile or atrophic vaginitis responds to topical estrogen. There is no evidence that administration of estrogens delays the progression of atherosclerosis in postmenopausal women. There is abundant evidence that administration of estrogen to postmenopausal women prevents bone loss (protects against osteoporosis) and also prevents vertebral and femoral bone fractures.⁷⁸ Estrogens are administered to decrease milk production in the postpartum period. The presence of receptors for estrogen increases the likelihood of a palliative response to estrogen therapy in women with metastatic breast cancer. An important use of estrogens is in combination with progestins as oral contraceptives.

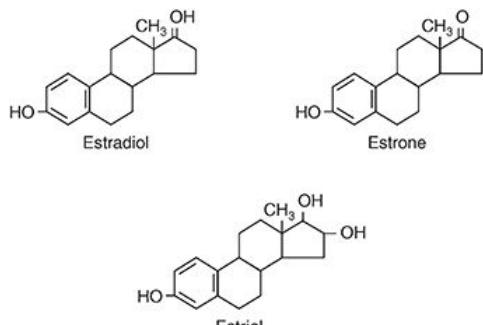


FIGURE 40.5 Estrogens.

Route of Administration

The absorption of most estrogens and their derivatives from the gastrointestinal tract is prompt and nearly complete. Metabolism in the liver, however, limits the effectiveness of orally administered estrogens. Topical and IM administration of estrogens is also effective. Radioimmunoassay methods are highly specific and sensitive for measuring the plasma concentrations of estrogens.

Side Effects

The most frequent unpleasant symptom associated with the use of estrogens is nausea. Large doses of estrogens may cause retention of sodium and water, which is particularly undesirable in patients with cardiac or renal disease. There is an increased incidence of vaginal and cervical adenocarcinoma in daughters of mothers treated with diethylstilbestrol or other synthetic estrogens during the first trimester of pregnancy. Most of the affected women have been 20 to 25 years old when diagnosed. Use of estrogen by postmenopausal women increases the risk of developing endometrial cancer.

Antiestrogens

Clomiphene and tamoxifen act as antiestrogens by binding to estrogen receptors (Figure 40.6). Tamoxifen is administered for a period of 5 years to postmenopausal women with breast cancer that was characterized by estrogen-responsive receptors. It is of interest that tamoxifen has estrogenic activity in some tissues, including bone. The loss of normal feedback inhibition of estrogen synthesis causes an increased secretion of gonadotropins. The most prominent effect on increased plasma concentrations of gonadotropins is the enlargement of the ovaries and enhancement of fertility in otherwise infertile women. Endometrial stimulation and an increased incidence of temperature disturbances ("hot flashes") may accompany treatment with tamoxifen.

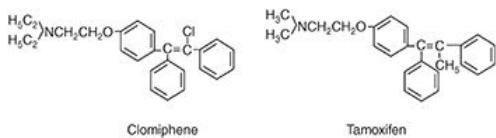


FIGURE 40.6 Antiestrogens.

Tissue-Specific Estrogens

Raloxifene is a nonsteroidal benzothiophene that acts as a selective estrogen-receptor modulator.⁷⁹ In this regard, raloxifene preserves the beneficial effects of estrogens (prevention of bone loss and lowering of plasma cholesterol concentrations) without any associated effects on reproductive organs. For example, endometrial stimulation does not accompany treatment with raloxifene. Tissue-specific estrogen agonist or antagonist actions of raloxifene may be related to estrogen receptor-mediated gene activation.

Progesterone

Orally active derivatives of progesterone are designated **progestins** (Figure 40.7). Progestins are often combined with estrogens as oral contraceptives. Dysfunctional uterine bleeding can be treated with small doses of a progestin for a few days, with the goal being induction of progesterone-withdrawal bleeding. Progestins, like estrogens, are effective in suppressing lactation in the immediate postpartum period. Palliative treatment of metastatic endometrial carcinoma is achieved with progestins. Absorption of progestins from the gastrointestinal tract is rapid, but hepatic first-pass metabolism is extensive.

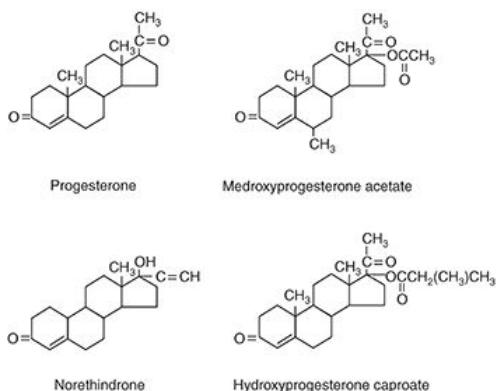


FIGURE 40.7 Progestins.

Antiprogestins

Antiprogestins inhibit the hormonal effects of progesterone and are the most effective and safest means of medical abortion.⁸⁰ In this regard, mifepristone (RU 486) can be administered in a single oral dose to produce termination of pregnancy (Figure 40.8). The combination of mifepristone with a prostaglandin administered 48 hours later by IM injection (sulprostone), by vaginal suppository (gemeprost), or orally (misoprostol) has resulted in a rate of complete abortion approaching 100%. Mifepristone has been used as a postcoital contraceptive within 72 hours of unprotected intercourse. In addition to its antiprogestin properties, mifepristone has antiglucocorticoid activity and is useful in the treatment of patients with hypercortisolism. Side effects of mifepristone include vaginal bleeding, nausea, vomiting, abdominal pain, and fatigue.

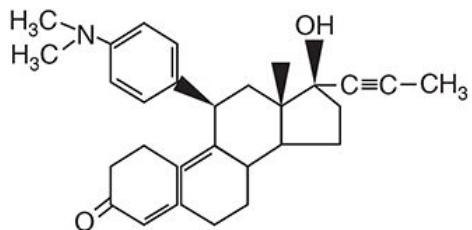


FIGURE 40.8 Mifepristone (RU 486).

Oral Contraceptives

Oral contraceptives are most often a combination of an estrogen and a progestin. This combination inhibits ovulation, presumably by preventing release of follicle-stimulating hormone by estrogen and luteinizing hormone by progesterone.

Side Effects

Estrogens in combined preparations are believed to be responsible for most, if not all, of the side effects of oral contraceptives. For example, estrogens seem to be responsible for the increased incidence of thromboembolism. Indeed, patients taking estrogens manifest increased blood concentrations of some clotting factors as well as increased platelet aggregation. Nausea, vomiting, weight gain, and breast discomfort resembling early pregnancy are attributed to the estrogen component of oral contraceptives. The incidence of myocardial infarction and stroke is increased in patients who chronically take oral contraceptives.⁸¹

Hypertension occurs in about 5% of women taking oral contraceptives chronically.⁸² This response probably reflects estrogen-induced increases in circulating plasma concentrations of renin and angiotensin, with associated retention of sodium and water.

Oral contraceptives containing high doses of estrogen may produce alterations in the glucose tolerance curves of patients with preclinical diabetes mellitus. These drugs increase the concentration of cholesterol in bile, which is consistent with an increased incidence of cholelithiasis. Benign hepatomas have been associated with the use of oral contraceptives. An increased incidence of breast cancer in patients taking oral contraceptives has not been documented. Depression of mood and fatigue have been attributed to the progestin component of oral contraceptives.

Androgens

Androgens are administered to males to stimulate the development and maintenance of secondary sexual characteristics (**Figure 40.9**). Testosterone is also prescribed to hypogonadal men who have evidence of androgen deficiency and a low serum testosterone concentration. The most common indication of androgen therapy in females is palliative management of metastatic breast cancer. Androgens enhance erythropoiesis by stimulation of renal production of erythropoietin as well as by direct dose-related stimulation of erythropoietin-sensitive elements in bone marrow. In addition, there is a drug-induced increase in 2,3-diphosphoglycerate levels, which decreases hemoglobin affinity for oxygen, thus enhancing the availability of oxygen to tissues. For these reasons, androgen therapy is often instituted in patients with aplastic anemia or hemolytic anemia. Androgen-anabolic steroids have been used in the treatment of chronic debilitating diseases. These drugs promote a feeling of well-being and may improve appetite when administered to patients with terminal illnesses. The efficacy of anabolic steroids to improve athletic performance is not documented and is condemned on ethical grounds. Certain androgens may be useful in the treatment of hereditary angioedema.

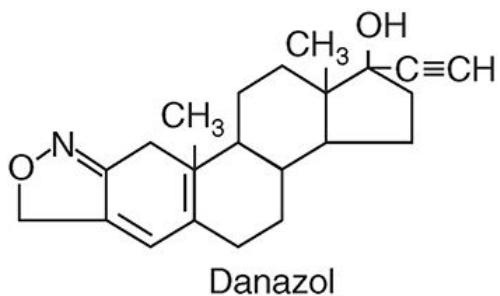


FIGURE 40.9 Androgens.

Route of Administration

About 99% of testosterone circulating in the plasma is bound to sex hormone–binding globulin. As a result, this globulin determines the concentration of free testosterone in the plasma and thus its elimination half-time, which is 10 to 20 minutes. Testosterone administered orally is readily absorbed but is metabolized so extensively by the liver that therapeutic effects do not occur. Alkylation of androgens at the 17 position retards their hepatic metabolism and permits such derivatives to be effective (see [Figure 40.9](#)). Alkylated testosterones are rarely prescribed because of their association with hepatic dysfunction. Intramuscular injection of esters of testosterone (ie, testosterone enanthate and testosterone cypionate), which are more lipophilic than testosterone alone, prolongs the duration of time that testosterone is present in the blood. Testosterone can also be delivered via patch and gels.

Side Effects

Dose-related cholestatic hepatitis and jaundice are particularly likely to accompany androgen therapy for palliation in neoplastic disease. Increases in the plasma alkaline phosphatase, hematocrit, and transaminase enzymes are also likely. Prolonged therapy (>1 year) with androgens, as for management of anemia, is associated with an increased incidence of hepatic cancer. Retention of sodium and water is also likely to accompany palliative treatment of cancer with high doses of androgens. Androgens increase the potency of coumarin anticoagulants and the likelihood of spontaneous hemorrhage. Androgens can decrease the concentration of thyroid-binding globulin in plasma and thus influence thyroid function tests.

Danazol

The low androgenic activity of danazol makes it the preferred androgen for treatment of hereditary angioedema (see [Figure 40.9](#)). In treated patients, there is a remission of symptoms as well as increased production of previously deficient plasma protein factors. As with other androgens, danazol therapy has been associated with abnormal liver function tests and jaundice. Danazol also decreases breast pain and nodularity in many women with fibrocystic breast disease. Symptoms of endometriosis are decreased, and fertility may be restored in danazol-treated women. In patients with hemophilia A, danazol increases factor VIII activity and decreases the incidence of hemorrhage.⁸³

Finasteride

Finasteride is a competitive 5- α -reductase inhibitor that does not bind to the androgen receptor ([Figure 40.10](#)).⁸⁴ As a result of this drug-induced enzyme inhibition, dihydrotestosterone production from testosterone does not occur. In the absence of dihydrotestosterone, the androgen effects on the prostate and skin do not occur. Finasteride is administered orally (5 mg once daily) for the treatment of benign prostatic hyperplasia. Treatment of male pattern baldness, hirsutism, and acne may represent other potentially useful applications for finasteride. There is no evidence that finasteride is beneficial in men with established prostate cancer. The elimination half-time after oral administration is 6 to 8 hours. The only important side effects of finasteride are related to decreased sexual function. Finasteride has no effect on serum lipids or bone density. Prostate-specific antigen concentrations are decreased by treatment with finasteride, introducing the concern that detection of prostate cancer could be masked in patients treated with this drug.

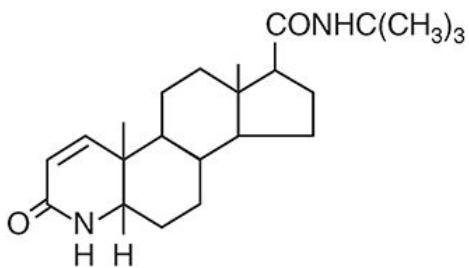


FIGURE 40.10 Finasteride.

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PART VIII Miscellaneous

Antimicrobials, Antiseptics, Disinfectants, and Management of Perioperative Infection

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Introduction

The excessive use of antimicrobials (antibiotics) for the treatment of conditions for which these drugs provide little or no benefit (upper respiratory tract infections, bronchitis) has contributed to the emergence of bacterial resistance. It is estimated that more than 25% of all prescriptions are written for conditions for which antibiotics are rarely indicated in ambulatory patients seen in physicians' offices.^{1,2} The overuse of antimicrobials for agricultural purposes dwarfs that for human use.³

Misuse of antibiotics in general is in contrast to the proven benefit of antibiotic prophylaxis for selected surgical procedures, which has been part of a national initiative to enhance compliance, the Surgical Care Improvement Project (SCIP). The SCIP, based originally on the Surgical Infection Project, was designed to combat a perceived national crisis of preventable surgical site infections, identified in the 1990s, which were associated with doubled risk of mortality, 60% higher likelihood of spending time in an intensive care unit, and fivefold risk of readmission.⁴ The original SCIP goal was a 25% reduction in surgical site infection by 2010.⁵ When this goal was not met, a subsequent goal of 25% reduction was set for 2013. Although data analysis in 2012 appeared promising, as a 20% reduction had been achieved, this reduction plateaued in the following years. The failure to meet these important but daunting goals has been attributed to several factors including a delayed launch, following inappropriate outcome variables, and outcome data that were biased by the "pay-for-performance" initiative.⁶ In 2015, the SCIP measures were retired, and The Joint Commission implemented the ORYX Performance Measures. Under The Joint Commission, hospital organizations are allowed to choose targeted surgical site infections surveillances based on their own risk assessments but are not required to include all surgical procedures.⁷

The baseline risk for perioperative infection is highly dependent on factors that require risk adjustment in clinical trials and consideration in clinical care. Patient-related risk factors for surgical site infection include extremes of age (younger than 5 and older than 65 years), higher American Society of Anesthesiologists physical status score, poor nutritional status, obesity, diabetes mellitus and perioperative glycemic control, peripheral vascular disease, tobacco use, coexistent infections, altered immune response, corticosteroid therapy, preoperative skin preparation (surgical scrub and hair removal), and length of preoperative hospitalization. Institutional variables include surgical experience and technique (ie, open vs laparoscopic), duration of procedure, quantity of blood loss, hospital environments including sterilization of instruments, and maintenance of perioperative normothermia.^{8–10} Some risk factors are surgery specific, such as the creation of an ostomy in bowel surgery and use of bilateral mammary arteries in coronary artery bypass grafting.

Of the aforementioned variables, few are modifiable at the time of surgery. For example, good perioperative glucose control can reduce infection risk. Perioperative glucose control has been studied in a variety of surgeries. In the cardiothoracic surgery population, it is associated with about a 50% decrease in deep sternal infection.¹¹ Continuous insulin infusion was associated with an additional reduction in surgical site infection compared to intermittent subcutaneous injection.¹² These findings have been generalized to bowel surgery where patients whose glucose was maintained below 200 mg/dL for 48 hours after surgery compared with those having concentrations greater than 200 mg/dL had significantly fewer surgical site infections (29.7% vs 14.3%).¹³ However, intensive insulin regimens designed to keep blood sugar ultralow have shown higher hypoglycemia and mortality compared to conventional treatment.¹⁴ In a recent meta-analysis of 15 studies, there was a benefit of intensive compared to conventional glucose monitoring

protocols in the prevention of surgical site infection (odds ratio 0.43).¹⁵ In this analysis, there was a higher risk of hypoglycemic episodes but no increase in the risk of death.

Although more difficult to achieve, smoking cessation is a perioperative goal. Perioperative education on smoking cessation by surgeons and anesthesiologists during preoperative evaluation is important. The preoperative period has been called a “teachable moment,” and even brief smoking cessation can reduce infection risk.¹⁶ A meta-analysis of four studies that have assessed the effect of 4 to 8 weeks of preoperative smoking cessation demonstrates a risk reduction of approximately 50%.¹⁷ Although electronic cigarettes do not contain tobacco, they do contain nicotine and other chemicals that have thus far shown to decrease wound healing and cutaneous blood flow.¹⁸ Whether electronic cigarettes have a similar impact on surgical site infection risk remains to be seen.

The anesthesiologist should contribute to the maintenance of perioperative normothermia. It is logical that hypothermia will result in peripheral vasoconstriction, decreased wound oxygen tension, and recruitment of leukocytes, favoring infection and impaired healing. In a meta-analysis of trials comparing intraoperative warming to control, warming was associated with a 64% decrease in surgical site infections.¹⁹ Prewarming patients before surgery reduces the peripheral-to-core temperature gradient and has the added advantage of making placement of intravenous (IV) lines easier because of peripheral vasodilation. Active prewarming of volunteers for 2 hours resulted in maintenance of core temperatures above 36°C for 60 minutes of general anesthesia at ambient temperature, whereas core temperatures in unwarmed subjects dropped an average of 1.9°C to below 35°C.

Immunosuppression on the basis of long-term use of corticosteroids is considered a risk factor for surgical site infection.²⁰ In a study of surgical site infection following lumbar fusion surgery, chronic oral steroid use in patients older than 65 years of age was found to significantly increase the risk of surgical site infections at 90 days and 1 year.²¹ Similarly, preoperative chemotherapy and corticosteroid use were independent predictors of cranial surgical site infections even when the data was controlled for leukopenia.²² There is clear evidence that a single dose of corticosteroid given to prevent nausea and vomiting and reduce pain does not promote infection. For example, in a study of open abdominal surgery for gynecologic cancer, there were no excess wound infections in patients treated with a single dose of dexamethasone for nausea and vomiting prophylaxis.²³

Antimicrobial Prophylaxis for Surgical Procedures

The use of antimicrobial prophylaxis in surgery involves a risk-to-benefit evaluation, which varies depending on the nature of the operative procedure. Previous SCIP measures retired in 2015 recommended the IV administration of prophylactic antimicrobials within 1 hour of surgical incision. This broadly accepted recommendation could not be substantiated after a systematic review and meta-analysis of all major medical databases from 1990 to 2016. Although administration of antibiotic prophylaxis more than 120 minutes before or after incision was associated with a higher risk of surgical site infections, there was no differential effect within the 120-minute time frame prior to incision.²⁴ Ideally, tissue concentration of the antibiotic should exceed the minimum inhibitory concentration associated with the procedure and/or patient characteristics from the time of incision to the completion of surgery. For short-acting antibiotics, this may require redosing (**Table 41.1**) especially when blood loss is greater than 1,500 mL.²⁵ Antibiotic treatment is not recommended for longer than 24 hours. This recommendation is based on findings of no benefit to prolonged dosing but rather an increased incidence of drug-resistant organisms.

TABLE 41.1 Recommended doses and redosing intervals for commonly used antimicrobials for surgical prophylaxis ^a				
	Recommended Dose		Half-life in adults with normal renal function (hours)	Recommended redosing interval (from initiation of preoperative dose; hours ^d)
Antimicrobial	Adults ^b	Pediatrics ^c		
Ampicillin-	3 g (ampicillin	50 mg/kg of the	0.8-1.3	2

sulbactam	2 g/sulbactam 1 g)	ampicillin component		
Ampicillin	2 g	50 mg/kg	1-1.9	2
Aztreonam	2 g	30 mg/kg	1.3-2.4	4
Cefazolin	2 g, 3 g for patients weighing \geq 120 kg	30 mg/kg	1.2-2.2	4
Cefuroxime	1.5 g	50 mg/kg	1-2	4
Cefotaxime	1 g ^e	50 mg/kg	0.9-1.7	3
Cefoxitin	2 g	40 mg/kg	0.7-1.1	2
Cefotetan	2 g	40 mg/kg	2.8-4.6	6
Ceftriaxone	2 g ^f	50-75 mg/kg	5.4-10.9	NA
Ciprofloxacin ^g	400 mg	10 mg/kg	3-7	NA
Clindamycin	900 mg	10 mg/kg	2-4	6
Ertapenem	1 g	15 mg/kg	3-5	NA
Fluconazole	400 mg	6 mg/kg	30	NA
Gentamicin ^h	5 mg/kg based on dosing weight (single dose)	2.5 mg/kg based on dosing weight	2-3	NA
Levofloxacin ^g	500 mg	10 mg/kg	6-8	NA
Metronidazole	500 mg	15 mg/kg Neonates weighing <1,200 g should receive a single 7.5-mg/kg dose.	6-8	NA
Moxifloxacin ^g	400 mg	10 mg/kg	8-15	NA
Piperacillin-tazobactam	3.375 g	Infants 2-9 mo: 80 mg/kg of the piperacillin component Children >9 mo and \leq 40 kg: 100 mg/kg of the piperacillin component	0.7-1.2	2
Vancomycin	15 mg/kg	15 mg/kg	4-8	NA
<i>Oral antibiotics for colorectal surgery prophylaxis (used in conjunction with a mechanical bowel preparation)</i>				
Erythromycin base	1 g	20 mg/kg	0.8-3	NA
Metronidazole	1 g	15 mg/kg	6-10	NA
Neomycin	1 g	15 mg/kg	2-3 (3% absorbed under normal gastrointestinal conditions)	NA

^aFrom Bratzler DW, Dellinger EP, Olsen KM, et al; American Society of Health-System Pharmacists; Infectious Diseases Society of America; Surgical Infection Society; Society for Healthcare Epidemiology of

America. Clinical practice guidelines for antimicrobial prophylaxis in surgery. *Am J Health Syst Pharm.* 2013;70(3):195–283. Reproduced by permission of American Society of Health-System Pharmacists, Inc.
^bAdult doses are obtained from the studies cited in each section. When doses differed between studies, expert opinion used the most often recommended dose.

^cThe maximum pediatric dose should not exceed the usual adult dose.

^dFor antimicrobials with a short half-life (eg, cefazolin, cefoxitin) used before long procedures, redosing in the operating room is recommended at an interval of approximately 2 times the half-life of the agent in patients with normal renal function. Recommended redosing intervals marked as “not applicable” (NA) are based on typical case length; for unusually long procedures, redosing may be needed.

^eAlthough U.S. Food and Drug Administration–approved package insert labeling indicates 1 g, 14 experts recommend 2 g for obese patients.

^fWhen used as a single dose in combination with metronidazole for colorectal procedures.

^gAlthough fluoroquinolones have been associated with an increased risk of tendinitis/tendon rupture in all ages, use of these agents for single-dose prophylaxis is generally safe.

^hIn general, gentamicin for surgical antibiotic prophylaxis should be limited to a single dose given preoperatively. Dosing is based on the patient’s actual body weight. If the patient’s actual weight is more than 20% above ideal body weight (IBW), the dosing weight (DW) can be determined as follows: DW = IBW + 0.4 (actual weight – IBW).

The antibiotic chosen should be appropriate for the most likely microorganism related to the procedure and patient characteristics.²⁶ For clean elective surgical procedures such as mastectomy and thyroidectomy in which no tissue (other than the skin) carrying an indigenous flora is penetrated, the risks of routine antimicrobial prophylaxis outweigh the possible benefits. The predominant organisms causing surgical site infections after clean procedures are skin flora (*Staphylococcus aureus* and *Staphylococcus epidermidis*). In clean-contaminated procedures, including abdominal procedures and solid organ transplantation, the most common organisms include gram-negative rods and enterococci in addition to skin flora.²⁷ Antibiotic recommendations for specific procedure prophylaxis can be found in **Table 41.2**.²⁶ Subspecialty societies have created many enhanced recovery after surgery guidelines, where details on antibiotic recommendations can be found.^{28–33}

TABLE 41.2

Common antimicrobials used for prophylaxis in various surgical settings^{a,f}

Type of procedure	Recommended agents ^{b,c}	Alternative agents in patients with β-lactam allergy	Strength of evidence ^d
Cardiac			
Coronary artery bypass	Cefazolin, cefuroxime	Clindamycin, ^e vancomycin ^e	A
Cardiac device insertion procedures (eg, pacemaker implantation)	Cefazolin, cefuroxime	Clindamycin, vancomycin	A
Ventricular assist devices	Cefazolin, cefuroxime	Clindamycin, vancomycin	C
Thoracic			
Noncardiac procedures, including lobectomy, pneumonectomy, lung resection, and thoracotomy	Cefazolin, ampicillin-sulbactam	Clindamycin, ^e vancomycin ^e	A
Video-assisted thoracoscopic surgery	Cefazolin, ampicillin-sulbactam	Clindamycin, ^e vancomycin ^e	C
Gastrointestinal			

Procedures involving entry into lumen of gastrointestinal tract (bariatric, pancreaticoduodenectomy ^g)	Cefazolin	Clindamycin or vancomycin + aminoglycoside ^h or aztreonam or fluoroquinolone ^{i,j,k}	A
Procedures without entry into gastrointestinal tract (antireflux, highly selective vagotomy) for high-risk patients	Cefazolin	Clindamycin or vancomycin + aminoglycoside ^h or aztreonam or fluoroquinolone ^{i,j,k}	A
Biliary tract			
Open procedure	Cefazolin, cefoxitin, cefotetan, ceftriaxone, ^l ampicillin-sulbactam ⁱ	Clindamycin or vancomycin + aminoglycoside ^h or aztreonam or fluoroquinolone ^{i,j,k} Metronidazole + aminoglycoside ^h or fluoroquinolone ^{i,j,k}	A
Laparoscopic procedure			
Elective, low-risk ^m	None	None	A
Elective, high-risk ^m	Cefazolin, cefoxitin, cefotetan, ceftriaxone, ^l ampicillin-sulbactam ⁱ	Clindamycin or vancomycin + aminoglycoside ^h or aztreonam or fluoroquinolone ^{i,j,k} Metronidazole + aminoglycoside ^h or fluoroquinolone ^{i,j,k}	A
Appendectomy for uncomplicated appendicitis	Cefoxitin, cefotetan, cefazolin + metronidazole	Clindamycin + aminoglycoside ^h or aztreonam or fluoroquinolone ^{i,j,k} Metronidazole + aminoglycoside ^h or fluoroquinolone ^{i,j,k}	A
Small intestine			
Nonobstructed	Cefazolin	Clindamycin + aminoglycoside ^h or aztreonam or fluoroquinolone ^{i,j,k}	C
Obstructed	Cefazolin + metronidazole, cefoxitin, cefotetan	Metronidazole + aminoglycoside ^h or fluoroquinolone ^{i,j,k}	C
Hernia repair (hernioplasty and herniorrhaphy)	Cefazolin	Clindamycin, vancomycin	A
Colorectal ⁿ	Cefazolin + metronidazole, cefoxitin, cefotetan, ampicillin-sulbactam, ⁱ ceftriaxone + metronidazole, ^o ertapenem	Clindamycin + aminoglycoside ^h or aztreonam or fluoroquinolone ^{i,j,k}	A

		metronidazole + aminoglycoside ^h or fluoroquinolone ^{i,j,k}	
Head and neck			
Clean	None	None	B
Clean with placement of prosthesis (excludes tympanostomy tubes)	Cefazolin, cefuroxime	Clindamycin ^e	C
Clean-contaminated cancer surgery	Cefazolin + metronidazole, cefuroxime + metronidazole, ampicillin-sulbactam	Clindamycin ^e	A
Other clean-contaminated procedures with the exception of tonsillectomy and functional endoscopic sinus procedures	Cefazolin + metronidazole, cefuroxime + metronidazole, ampicillin-sulbactam	Clindamycin ^e	B
Neurosurgery			
Elective craniotomy and cerebrospinal fluid-shunting procedures	Cefazolin	Clindamycin, ^e vancomycin ^e	A
Implantation of intrathecal pumps	Cefazolin	Clindamycin, ^e vancomycin ^e	C
Cesarean delivery	Cefazolin	Clindamycin + aminoglycoside ^h	A
Hysterectomy (vaginal or abdominal)	Cefazolin, cefotetan, cefoxitin, ampicillin-sulbactam	Clindamycin or vancomycin + aminoglycoside ^h or aztreonam or fluoroquinolone ^{i,j,k} Metronidazole + aminoglycoside ^h or fluoroquinolone ^{i,j,k}	A
Ophthalmic	Topical neomycin—polymyxin B—gramicidin or fourth-generation topical fluoroquinolones (gatifloxacin or moxifloxacin) given as 1 drop every 5-15 min for 5 doses ^p Addition of cefazolin 100 mg by subconjunctival injection or intracameral cefazolin 1-2.5 mg or cefuroxime 1 mg at the end of procedure is optional	None	B
Orthopedic			
Clean operations involving hand, knee, or foot and not involving implantation of foreign materials	None	None	C
Spinal procedures with and	Cefazolin	Clindamycin, ^e vancomycin ^e	A

without instrumentation			
Hip fracture repair	Cefazolin	Clindamycin, ^e vancomycin ^e	A
Implantation of internal fixation devices (eg, nails, screws, plates, wires)	Cefazolin	Clindamycin, ^e vancomycin ^e	C
Total joint replacement	Cefazolin	Clindamycin, ^e vancomycin ^e	A
Urologic			
Lower tract instrumentation with risk factors for infection (includes transrectal prostate biopsy)	Fluoroquinolone, ^{i,j,k} trimethoprim-sulfamethoxazole, cefazolin	Aminoglycoside ^h with or without clindamycin	A
Clean without entry into urinary tract	Cefazolin (the addition of a single dose of an aminoglycoside may be recommended for placement of prosthetic material [eg, penile prosthesis])	Clindamycin, ^e vancomycin ^e	A
Involving implanted prosthesis	Cefazolin ± aminoglycoside, cefazolin ± aztreonam, ampicillin-sulbactam	Clindamycin ± aminoglycoside or aztreonam, vancomycin ± aminoglycoside or aztreonam	A
Clean with entry into urinary tract	Cefazolin (the addition of a single dose of an aminoglycoside may be recommended for placement of prosthetic material [eg, penile prosthesis])	Fluoroquinolone, ^{i,j,k} aminoglycoside ^h with or without clindamycin	A
Clean-contaminated	Cefazolin + metronidazole, cefoxitin	Fluoroquinolone, ^{i,j,k} aminoglycoside ^h + metronidazole or clindamycin	A
Vascular^g			
Heart, lung, heart-lung transplantation ^r	Cefazolin	Clindamycin, ^e vancomycin ^e	A
Heart transplantation ^s	Cefazolin	Clindamycin, ^e vancomycin ^e	A (based on cardiac procedures)
Lung and heart-lung transplantation ^{s,t}	Cefazolin	Clindamycin, ^e vancomycin ^e	A (based on cardiac procedures)
Liver transplantation ^{r,u}	Piperacillin-tazobactam, cefotaxime + ampicillin	Clindamycin or vancomycin + aminoglycoside ^h or aztreonam or fluoroquinolone ^{i,j,k}	B
Pancreas and pancreas-kidney transplantation ^s	Cefazolin, fluconazole (for patients at high risk for fungal infection [eg, those with enteric drainage of the pancreas])	Clindamycin or vancomycin + aminoglycoside ^h or aztreonam or fluoroquinolone ^{i,j,k}	A
Plastic surgery	Cefazolin	Clindamycin or vancomycin + aminoglycoside ^h or	A

		aztreonam or fluoroquinolone ^{ij,k}	
Clean with risk factors or clean-contaminated	Cefazolin, ampicillin-sulbactam	Clindamycin, ^e vancomycin ^e	C

^aFrom Bratzler DW, Dellinger EP, Olsen KM, et al; American Society of Health-System Pharmacists; Infectious Diseases Society of America; Surgical Infection Society; Society for Healthcare Epidemiology of America. Clinical practice guidelines for antimicrobial prophylaxis in surgery. *Am J Health Syst Pharm*. 2013;70(3):195–283. Reproduced by permission of American Society of Health-System Pharmacists, Inc.

^bThe antimicrobial agent should be started within 60 minutes before surgical incision (120 min for vancomycin or fluoroquinolones). Although single-dose prophylaxis is usually sufficient, the duration of prophylaxis for all procedures should be less than 24 hours. If an agent with a short half-life is used (eg, cefazolin, cefoxitin), it should be readministered if the procedure duration exceeds the recommended redosing interval (from the time of initiation of the preoperative dose [see [Table 41.2](#)]). Readministration may also be warranted if prolonged or excessive bleeding occurs or if there are other factors that may shorten the half-life of the prophylactic agent (eg, extensive burns). Readministration may not be warranted in patients in whom the half-life of the agent may be prolonged (eg, patients with renal insufficiency or failure).

^cFor patients known to be colonized with methicillin-resistant *Staphylococcus aureus*, it is reasonable to add a single preoperative dose of vancomycin to the recommended agent(s).

^dStrength of evidence that supports the use or nonuse of prophylaxis is classified as A (levels I-III), B (levels IV-VI), or C (level VII). Level I evidence is from large, well-conducted, randomized controlled clinical trials. Level II evidence is from small, well-conducted, randomized controlled clinical trials. Level III evidence is from well-conducted cohort studies. Level IV evidence is from well-conducted case control studies. Level V evidence is from uncontrolled studies that were not well conducted. Level VI evidence is conflicting evidence that tends to favor the recommendation. Level VII evidence is expert opinion.

^eFor procedures in which pathogens other than staphylococci and streptococci are likely, an additional agent with activity against those pathogens could be considered. For example, if there are surveillance data showing that gram-negative organisms are a cause of surgical-site infections (SSIs) for the procedure, practitioners may consider combining clindamycin or vancomycin with another agent (cefazolin if the patient is not β -lactam allergic; aztreonam, gentamicin, or single-dose fluoroquinolone if the patient is β -lactam allergic).

^fProphylaxis should be considered for patients at highest risk for postoperative gastroduodenal infections, such as those with increased gastric pH (eg, those receiving histamine H₂-receptor antagonists or proton-pump inhibitors), gastroduodenal perforation, decreased gastric motility, gastric outlet obstruction, gastric bleeding, morbid obesity, or cancer. Antimicrobial prophylaxis may not be needed when the lumen of the intestinal tract is not entered.

^gConsider additional antimicrobial coverage with infected biliary tract. See the biliary tract procedures section of this table.

^hGentamicin or tobramycin.

ⁱDue to increasing resistance of *Escherichia coli* to fluoroquinolones and ampicillin-sulbactam, local population susceptibility profiles should be reviewed prior to use.

^jCiprofloxacin or levofloxacin.

^kFluoroquinolones are associated with an increased risk of tendonitis and tendon rupture in all ages. However, this risk would be expected to be quite small with single-dose antibiotic prophylaxis. Although the use of fluoroquinolones may be necessary for surgical antibiotic prophylaxis in some children, they are not drugs of first choice in the pediatric population due to an increased incidence of adverse events as compared with controls in some clinical trials.

^lCeftriaxone use should be limited to patients requiring antimicrobial treatment for acute cholecystitis or acute biliary tract infections, which may not be determined prior to incision, not patients undergoing cholecystectomy for noninfected biliary conditions, including biliary colic or dyskinesia without infection.

^mFactors that indicate a high risk of infectious complications in laparoscopic cholecystectomy include emergency procedures, diabetes, long procedure duration, intraoperative gallbladder rupture, age of >70

years, conversion from laparoscopic to open cholecystectomy, American Society of Anesthesiologists classification of 3 or greater, episode of colic within 30 days before the procedure, reintervention in less than 1 month for noninfectious complication, acute cholecystitis, bile spillage, jaundice, pregnancy, nonfunctioning gallbladder, immunosuppression, and insertion of prosthetic device. Because a number of these risk factors are not possible to determine before surgical intervention, it may be reasonable to give a single dose of antimicrobial prophylaxis to all patients undergoing laparoscopic cholecystectomy.

^bFor most patients, a mechanical bowel preparation combined with oral neomycin sulfate plus oral erythromycin base or with oral neomycin sulfate plus oral metronidazole should be given in addition to IV prophylaxis.

^cWhere there is increasing resistance to first- and second-generation cephalosporins among gram-negative isolates from SSIs, a single dose of ceftriaxone plus metronidazole may be preferred over the routine use of carbapenems.

^dThe necessity of continuing topical antimicrobials postoperatively has not been established.

^eProphylaxis is not routinely indicated for brachiocephalic procedures. Although there are no data in support, patients undergoing brachiocephalic procedures involving vascular prostheses or patch implantation (eg, carotid endarterectomy) may benefit from prophylaxis.

^fThese guidelines reflect recommendations for perioperative antibiotic prophylaxis to prevent SSIs and do not provide recommendations for prevention of opportunistic infections in immunosuppressed transplantation patients (eg, for antifungal or antiviral medications).

^gPatients who have left ventricular assist devices as a bridge and who are chronically infected might also benefit from coverage of the infecting microorganism.

^hThe prophylactic regimen may need to be modified to provide coverage against any potential pathogens, including gram-negative (eg, *P aeruginosa*) or fungal organisms, isolated from the donor lung or the recipient before transplantation. Patients undergoing lung transplantation with negative pretransplantation cultures should receive antimicrobial prophylaxis as appropriate for other types of cardiothoracic surgeries. Patients undergoing lung transplantation for cystic fibrosis should receive 7-14 days of treatment with antimicrobials selected according to pretransplantation culture and susceptibility results. This treatment may include additional antibacterial or antifungal agents.

ⁱThe prophylactic regimen may need to be modified to provide coverage against any potential pathogens, including vancomycin-resistant enterococci, isolated from the recipient before transplantation.

Because of their wide therapeutic index and low incidence of side effects, cephalosporins (most often a cost-effective first-generation cephalosporin such as cefazolin) are the antimicrobials of choice for surgical procedures in which skin flora and normal flora of the gastrointestinal and genitourinary tracts are the most likely pathogens. Patients with documented immunoglobulin E (IgE) reaction to cephalosporins are rare and often mistaken for more common intolerances such as nausea or yeast infection. The IgE-mediated anaphylactic reactions to antimicrobials usually occur 30 to 60 minutes after dosing and often include urticaria, bronchospasm, and hemodynamic collapse. This reaction is a life-threatening emergency that precludes subsequent use of the drug. Cephalosporins can safely be used in patients with an allergic reaction to penicillins that is not an IgE-mediated reaction (eg, anaphylaxis, urticaria, bronchospasm) or exfoliative dermatitis (Stevens-Johnson syndrome, toxic epidermal necrolysis).³⁴ Although early reports of cross-reactivity were high due to contaminated drug lots, the actual rate of cross-reactivity is only 1%.³⁴ However, the consequences of true anaphylaxis are severe. Patients should be carefully questioned about the nature of any drug allergy. Documentation of allergy should be separated from medication intolerances in institutional databases where possible. For example, 90% of patients who report a penicillin allergy are found to be incorrect with comprehensive testing. This is a barrier to antibiotic stewardship, and it exposes the patient to harm from a potentially more toxic or less effective antibiotic.³⁵ In patients with documented IgE-mediated anaphylactic reactions, β-lactam antibiotics can usually be substituted with clindamycin or vancomycin.²⁶ Vancomycin may also be considered when methicillin-resistant *S aureus* (MRSA) is considered likely, for example, in children or elderly patients known to be colonized with MRSA. Nasal application of mupirocin

has been considered as an alternative and has been found to be effective in eliminating MRSA colonization in adults and children. It is U.S. Food and Drug Administration approved for eradication of colonization in adults and health care workers. Treatment with mupirocin is effective in reducing *S aureus* infection in documented carriers. Preoperative screening is recommended to identify high-risk patients who would benefit from decolonization and to guide appropriate preoperative antibiotic selection for those with resistant organisms. Routine prophylaxis with vancomycin is not recommended for any patient population in the absence of documented or highly suspected colonization or infection with MRSA (recent hospitalization of nursing home stay and hemodialysis patients) or known IgE-mediated response to β -lactam antibiotics.³⁶ The recommendation against routine prophylaxis with vancomycin is due to concerns about selection of resistant organisms, its risk of inducing hemodynamic instability due to histamine release (red man syndrome; [Figure 41.1](#)) if given rapidly, and evidence that vancomycin is less effective than cefazolin in methicillin-susceptible *S aureus*.^{37,38} With increasing prevalence of MRSA among patients, dual antibiotic regimens such as vancomycin with cefazolin supplementation has been proposed as prophylaxis against surgical site infections, particularly in joint replacement surgeries. There are limited studies supporting any clear advantage in reductions in surgical site infections without increased risk of adverse effects such as acute kidney injury with dual antibiotic regimens.³⁹ The Australian Surgical Antibiotic Prophylaxis trial is currently underway and should shed more light in the coming years on the combination of vancomycin and cefazolin for surgical antibiotic prophylaxis.⁴⁰ New vaccines and antibody therapies are in development to help prevent and treat infection where antibiotics are not effective.⁴¹

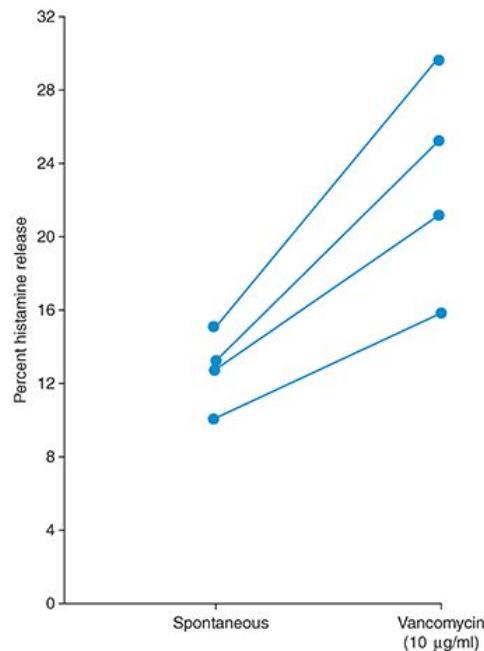


FIGURE 41.1 Histamine release (%) from dispersed human cutaneous mast cells after the administration of vancomycin. Reprinted with permission from Levy JH, Kettlekamp N, Goertz P, et al. Histamine release by vancomycin. A mechanism for hypotension in man. *Anesthesiology*. 1987;67(1):122-125. Copyright © 1987 American Society of Anesthesiologists, Inc.

Clean-contaminated procedures such as colorectal and abdominal surgeries require additional coverage for gram-negative rods and anaerobes in addition to skin flora. Metronidazole can be added to cefazolin or cefoxitin, cefotetan, ampicillin-sulbactam, ertapenem, or ceftriaxone. Bowel preparation with oral antimicrobials has been studied as a potentially less costly alternative. Mechanical bowel preparation alone does not reduce infection, but selective decontamination of the digestive tract with oral topical polymyxin, tobramycin, and amphotericin eradicates the colonization gram-negative microorganisms, *S aureus*, and yeasts from oral cavity to rectum. Vancomycin would be active against MRSA but is not recommended

because gram-positive flora plays an important role in the resistance to colonization.⁴² In a meta-analysis of eight studies, the combination of oral treatment and perioperative venous prophylaxis was found to be superior to IV prophylaxis alone in preventing surgical site infection and anastomotic leak. However, older studies found that oral antibiotics alone are not a solution. A randomized controlled study was stopped because of higher rate of infection in the oral neomycin and erythromycin group (41%) compared with the single-dose IV metronidazole and ceftriaxone group.⁴³ Another trial of oral metronidazole and kanamycin compared with the same medications given IV found an increased rate of postoperative sepsis and pseudomembranous colitis in the oral group.⁴⁴ Pseudomembranous colitis is the most frequent complication of prophylactic antimicrobials, including the IV cephalosporins. Additional toxicities are covered in [Table 41.3](#).

TABLE 41.3

Direct drug toxicity associated with administration of antimicrobials

Toxicity	Antimicrobial
Allergic reactions	All antimicrobials but most often with β -lactam derivatives
Nephrotoxicity	Aminoglycosides Polymyxins Amphotericin B
Neutropenia	Penicillins Cephalosporins Vancomycin
Inhibition of platelet aggregation	Penicillins (high doses)
Prolonged prothrombin time	Cephalosporins
Bone marrow suppression (aplastic anemia, pancytopenia)	Chloramphenicol Flucytosine Linezolid (reversible)
Hemolytic anemia	Chloramphenicol Sulfonamides Nitrofurantoin Primaquine
Agranulocytosis	Macrolides Trimethoprim-sulfamethoxazole
Leukopenia and thrombocytopenia (folate deficiency)	Trimethoprim
Normocytic normochromic anemia	Amphotericin B
Ototoxicity	Aminoglycosides Vancomycin (auditory neurotoxicity) Minocycline (vestibular toxicity)
Seizures	Penicillins and other β -lactams (high doses, azotemic patients, history of epilepsy) Metronidazole
Neuromuscular blockade	Aminoglycosides
Peripheral neuropathy	Nitrofurantoin (renal failure) Isoniazid (prevent with pyridoxine) Metronidazole
Benign intracranial hypertension	Tetracyclines
Optic neuritis	Ethambutol
Hepatotoxicity	Isoniazid Rifampin

	Tetracyclines (high doses) β-Lactam antimicrobials (high doses) Nitrofurantoin Erythromycin Sulfonamides
Increased plasma bilirubin concentrations	Quinupristin-dalfopristin Erythromycin
Gastrointestinal irritation	Tetracyclines
Prolongation of QTc interval	Erythromycin Fluoroquinolones
Exaggerated sympathomimetic effects in patients receiving monoamine oxidase inhibitors	Linezolid
Hyperkalemia	Trimethoprim-sulfamethoxazole
Tendinitis	Fluoroquinolones
Arthralgias and myalgias	Quinupristin-dalfopristin
Photosensitivity	Sulfonamides Tetracyclines Fluoroquinolones
Teratogenicity	Tetracyclines Metronidazole Rifampin Trimethoprim Fluoroquinolones

Antimicrobial Selection

Prompt identification of the causative organism is essential for the selection of appropriate antimicrobial drugs to treat ongoing infection. The efficacy of antimicrobial therapy depends on drug delivery to the site of infection. Body sites with poor blood flow and with low pH such as pressure and diabetic ulcers are difficult to treat. Antimicrobial therapy is more likely to be effective if infected material (foreign body, prosthesis) is removed. Infections behind obstructing lesions such as pneumonia behind a blocked bronchus will not respond to antimicrobials until the obstruction is relieved. Transport across the blood–brain barrier varies greatly among antimicrobials and is important to consider when prescribing an antibiotic for a neuraxial infection.

Nosocomial Infections

Nearly 80% of nosocomial infections occur in three sites (urinary tract, respiratory system, and bloodstream). The incidence of nosocomial infections is highly associated with the use of devices such as ventilators, vascular access catheters, and urinary catheters. Intravascular access catheters are the most common causes of bacteremia or fungemia in hospitalized patients.⁴⁵ The organism infecting access catheters most commonly comes from the colonized hub or lumen and reflect skin flora (*S aureus* and *S epidermidis*). Initial therapy of suspected intravascular catheter infection usually includes vancomycin because of the high incidence of MRSA and methicillin-resistant *S epidermidis* in the nosocomial environment. Central line-associated bloodstream infections account for 60% of all infections related to vascular access. Effective guidelines include care bundles to ensure application of evidence-based practices including hand hygiene, appropriate skin preparation, and barrier precautions.⁴⁶

Special Patient Groups

Parturients

Administration of antimicrobials during pregnancy introduces the question of safety for the mother and fetus (**Table 41.4**). Most antimicrobials cross the placenta and enter maternal milk. The immature fetal liver may lack enzymes necessary to metabolize certain drugs such that pharmacokinetics and toxicities in the fetus are often different from those in older children and adults. Teratogenicity is a concern when any drug is administered during early pregnancy. Increases in maternal blood volume, glomerular filtration rate, and hepatic metabolic activity may decrease plasma antimicrobial concentrations (10%-50%), especially late in pregnancy and in the early postpartum period. In some parturients, delayed gastric emptying may decrease absorption of orally administered antimicrobials.⁴⁷

TABLE 41.4

Antimicrobials in pregnancy

Drug	Maternal toxicity	Fetal toxicity	Excreted in colostrum
Considered safe			
Penicillins	Allergic reactions	None known	Trace
Cephalosporins	Allergic reactions	None known	Trace
Erythromycin base	Allergic reactions Gastrointestinal irritation	None known	Yes
Use cautiously			
Aminoglycosides	Ototoxicity Nephrotoxicity	Ototoxicity	Yes
Clindamycin	Allergic reactions Colitis	None known	Trace
Ethambutol	Optic neuritis	None known	Unknown
Isoniazid	Allergic reactions Hepatotoxicity	Neuropathy Seizures	Yes
Rifampin	Allergic reactions Hepatotoxicity	None known	Yes
Sulfonamides	Allergic reactions	Kernicterus (at term) Hemolysis (G6PD deficiency)	Yes
Avoid			
Metronidazole	Allergic reactions Alcohol intolerance Peripheral neuropathy	None known (teratogenic in animals)	Yes
Contraindicated			
Chloramphenicol	Bone marrow depression	Gray syndrome	Yes
Erythromycin estolate	Hepatotoxicity	None known	Yes
Nalidixic acid	Gastrointestinal irritation	Increased intracranial pressure	Unknown
Fluoroquinolones	Gastrointestinal irritation	Arthropathies (animals)	Unknown
Nitrofurantoin	Allergic reactions Peripheral neuropathy Gastrointestinal irritation	Hemolysis (G6PD deficiency)	Trace
Tetracyclines	Hepatotoxicity Nephrotoxicity	Tooth discoloration and dysplasia Impaired bone growth	Yes
Trimethoprim	Allergic reactions	Teratogenicity	Yes

Abbreviation: G6PD, glucose-6-phosphate dehydrogenase.

Elderly Patients

Physiologic changes that occur with increasing age can alter oral absorption (decreased gastric acidity, reduced gastrointestinal motility), distribution (increased total body fat, decreased plasma albumin concentrations), metabolism (decreased hepatic blood flow), and excretion (decreased glomerular filtration rate) of antimicrobials. Penicillins and cephalosporins, because of their large therapeutic index, obviate the need for significant changes in dosage schedules in elderly patients who have normal serum creatinine concentrations. Conversely, administration of aminoglycosides and vancomycin to elderly patients may require adjustments in dosing regimens. Measurement of plasma concentrations of antimicrobials and monitoring of renal function may be indicated when administering certain antimicrobials to elderly patients.

Human Immunodeficiency Virus-Infected Patients

There has been concern about increased risk of postoperative infection in human immunodeficiency virus-infected patients based on their increased risk for opportunistic infection in the setting of reduced T4 cell counts. Several recent studies have addressed this issue and produced conflicting results.⁴⁸⁻⁵⁰ Favorable results appear to be related to good preoperative control on an antiretroviral regimen with preserved T4 cell counts.⁵¹

Antibacterial Drugs Commonly Used in the Perioperative Period

Penicillins

The basic structure of penicillins is a dicyclic nucleus (aminopenicillanic acid) that consists of a thiazolidine ring connected to a β -lactam ring. The penicillins may be classified into subgroups because of their structure, β -lactamase susceptibility, and spectrum of activity. The bactericidal action of penicillins reflects the ability of these antimicrobials to interfere with the synthesis of peptidoglycan, which is an essential component of cell walls of susceptible bacteria. Penicillins also decrease the availability of an inhibitor of murein hydrolase such that the uninhibited enzyme can then destroy (lyse) the structural integrity of bacterial cell walls. Cell membranes of resistant gram-negative bacteria are in general resistant to penicillins because they prevent access to sites where synthesis of peptidoglycan is taking place.

Clinical Indications

Penicillin is the drug of choice for treatment of pneumococcal, streptococcal, and meningococcal infections. Gonococci have gradually become more resistant to penicillin, requiring higher doses for adequate treatment. Treatment of syphilis with penicillin is highly effective. Penicillin is the drug of choice for treating all forms of actinomycosis and clostridial infections causing gas gangrene.

Prophylactic administration of penicillin is highly effective against streptococcal infections, accounting for its value in patients with rheumatic fever. Transient bacteremia occurs in the majority of patients undergoing dental extractions, emphasizing the importance of prophylactic penicillin in patients with congenital or acquired heart disease or tissue implants undergoing dental procedures. Transient bacteremia may also accompany surgical procedures, such as tonsillectomy and operations on the genitourinary and gastrointestinal tracts and vaginal delivery.

Administration of high doses of penicillin G IV to patients with renal dysfunction may result in neurotoxicity and hyperkalemia (10 million units of penicillin G contains 16 mEq of potassium). If this amount of potassium introduces a risk to the patient, a sodium salt of penicillin G or a sodium salt of a similar penicillin, such as ampicillin or carbenicillin, can be substituted for the aqueous penicillin G.

Other drugs should not be mixed with penicillin as the combination may inactivate the antimicrobial. Intrathecal administration of penicillins is not recommended because these drugs are potent convulsants when administered by this route. Furthermore, arachnoiditis and encephalopathy may follow intrathecal penicillin administration.

Excretion

Renal excretion of penicillin is rapid (60%-90% of an intramuscular [IM] dose is excreted in the first hour), such that the plasma concentration decreases to 50% of its peak value within 1 hour after injection.

Approximately 10% is eliminated by glomerular filtration, and 90% is eliminated by renal tubular secretion. Anuria increases the elimination half-time of penicillin G approximately 10-fold.

Duration of Action

Methods to prolong the duration of action of penicillin include the simultaneous administration of probenecid, which blocks the renal tubular secretion of penicillin. Alternatively, the IM injection of poorly soluble salts of penicillin, such as procaine or benzathine, delays absorption and thus prolongs the duration of action. Procaine penicillin contains 120 mg of the local anesthetic for every 300,000 units of the antimicrobial. Possible hypersensitivity to procaine must be considered when selecting this form of the antimicrobial for administration.

Penicillinase-Resistant Penicillins

The major mechanism of resistance to the penicillins is bacterial production of β -lactamase enzymes that hydrolyze the β -lactam ring, rendering the antimicrobial molecule inactive. Methicillin, oxacillin, nafcillin, cloxacillin, and dicloxacillin are not susceptible to hydrolysis by staphylococcal penicillinases that would otherwise hydrolyze the cyclic amide bond of the β -lactam ring and render the antimicrobial inactive.

Specific indications for these drugs are infections caused by staphylococci known to produce this enzyme. Penetration of nafcillin into the central nervous system (CNS) is sufficient to treat staphylococcal meningitis. Parenteral methicillin has largely been superseded by oxacillin and nafcillin. Hemorrhagic cystitis and an allergic interstitial nephritis (hematuria, proteinuria) may accompany administration of methicillin. Hepatitis has been associated with high-dose oxacillin therapy. Renal excretion of methicillin, oxacillin, and cloxacillin is extensive. More than 80% of an IV dose of nafcillin is excreted in the bile, which may be an advantage when high-dose therapy is necessary in a patient with impaired renal function.

Oxacillin and nafcillin, unlike methicillin, are relatively stable in an acidic medium, resulting in adequate systemic absorption after oral administration. Nevertheless, variable absorption from the gastrointestinal tract often dictates a parenteral route of administration for treatment of serious infections caused by penicillinase-producing staphylococci. Cloxacillin and dicloxacillin are available only as oral preparations and may be preferable because they produce higher blood levels than do oxacillin and nafcillin.

Penicillinase-Susceptible Broad-Spectrum Penicillins (Second-Generation Penicillins)

Broad-spectrum penicillins, such as ampicillin, amoxicillin, and carbenicillin, have a wider range of activity than other penicillins, being bactericidal against gram-positive and gram-negative bacteria. They are, nevertheless, all inactivated by penicillinase produced by certain gram-negative and gram-positive bacteria. Therefore, these drugs are not effective against most staphylococcal infections.

Ampicillin

Ampicillin (α -aminobenzylpenicillin) has a broader range of activity than penicillin G. Its spectrum encompasses not only pneumococci, meningococci, gonococci, and various streptococci but also a number of gram-negative bacilli, such as *Haemophilus influenzae* and *Escherichia coli*. Ampicillin is stable in acid and thus is well absorbed after oral administration, although peak plasma concentrations are lower than those achieved after administration of penicillin V. Approximately 50% of an oral dose of ampicillin is excreted unchanged by the kidneys in the first 6 hours, emphasizing that renal function greatly influences the duration of action of this antimicrobial. Ampicillin also appears in the bile and undergoes enterohepatic circulation. Among the penicillins, ampicillin is associated with the highest incidence of skin rash (9%), which typically appears 7 to 10 days after initiation of therapy. Many of these rashes are due to protein impurities in the commercial preparation of the drug and do not represent true allergic reactions.

Amoxicillin

Amoxicillin is chemically identical to ampicillin except for an –OH substituent instead of an –H on the side chain. Its spectrum of activity is identical to that of ampicillin, but it is more efficiently absorbed from the gastrointestinal tract than ampicillin, and effective concentrations are present in the circulation for twice as long.

Extended-Spectrum Carboxypenicillins (Third-Generation Penicillins)

Carbenicillin

Carbenicillin (α -carboxybenzylpenicillin) results from the change from an amino to carboxy substituent on the side chain of ampicillin. The principal advantage of carbenicillin is its effectiveness in the treatment of infections caused by *Pseudomonas aeruginosa* and certain *Proteus* strains that are resistant to ampicillin. This antimicrobial is penicillinase susceptible and therefore ineffective against most strains of *S aureus*.

Carbenicillin is not absorbed from the gastrointestinal tract; therefore, it must be administered parenterally. The elimination half-time is approximately 1 hour and is prolonged to approximately 2 hours when there is hepatic or renal dysfunction. Approximately 85% of the unchanged drug is recovered in urine over 9 hours. Probenecid, by delaying renal excretion of the drug, increases the plasma concentration of carbenicillin by approximately 50%.

The sodium load administered with a large dose of carbenicillin (30–40 g) is considerable because greater than 10% of carbenicillin is sodium (about 5 mEq/g). Congestive heart failure may develop in susceptible patients in response to this acute drug-produced sodium load. Hypokalemia and metabolic alkalosis may occur because of obligatory excretion of potassium with the large amount of nonreabsorbable carbenicillin. Carbenicillin interferes with normal platelet aggregation such that bleeding time is prolonged but platelet count remains normal.

Extended-Spectrum Acylaminopenicillins (Fourth-Generation Penicillins)

The acylaminopenicillins (mezlocillin, piperacillin, azlocillin) have the broadest spectrum of activity of all the penicillins. Like the carboxypenicillins, the acylaminopenicillins are derivatives of ampicillin. These drugs are ineffective against penicillinase-producing strains of *S aureus*. The acylaminopenicillins have lower sodium content than the carboxypenicillins, but otherwise, the side effects are similar. Clinical studies have not demonstrated that these antimicrobials are superior to the carboxypenicillins.

Penicillin β -Lactamase Inhibitor Combinations

Clavulanic acid, sulbactam, and tazobactam are β -lactam compounds that have little intrinsic antimicrobial activity. However, these compounds bind irreversibly to the β -lactamase enzymes, which are produced by many bacteria, thus inactivating these enzymes and rendering the organisms sensitive to β -lactamase–susceptible penicillins. Clavulanic acid is available with oral amoxicillin, and parenteral ampicillin preparations have been combined with sulbactam. Likewise, parenteral piperacillin preparations have been combined with tazobactam.

Cephalosporins

Cephalosporins, like the penicillins, are bactericidal antimicrobials that inhibit bacterial cell wall synthesis and have a low intrinsic toxicity. These antimicrobials are derived from 7-aminocephalosporanic acid. Resistance to the cephalosporins, as to the penicillins, may be due to an inability of the antimicrobial to penetrate to its site of action. Bacteria can also produce cephalosporinases (β -lactamases), which disrupt the β -lactam structure of cephalosporins and thus inhibit their antimicrobial activity. Like the newer penicillins, the new cephalosporins have an extraordinarily broad spectrum of antimicrobial action but are expensive.

Individual cephalosporins differ significantly with respect to the extent of absorption after oral ingestion, severity of pain produced by IM injection, and protein binding. The IV administration of any of the cephalosporins can cause thrombophlebitis. Diacetyl metabolites of cephalosporins can occur and are associated with decreased antimicrobial activity.

A positive Coombs reaction frequently occurs in patients who receive large doses of cephalosporins. Hemolysis, however, is rarely associated with this response. Nephrotoxicity owing to cephalosporins, with

the exception of cephaloridine, is less frequent than after administration of aminoglycosides or polymyxins.

The incidence of allergic reactions in patients being treated with cephalosporins ranges from 1% to 10%. The majority of the allergic reactions consist of cutaneous manifestations, which occur 24 hours after drug exposure. Life-threatening anaphylaxis is estimated to occur in 0.02% of treated patients.⁵² Because the cephalosporins share immunologic cross-reactivity, patients who are allergic to one cephalosporin are likely to be allergic to others. The possibility of cross-reactivity between cephalosporins and penicillins seems to be very infrequent, and cephalosporins are often selected as alternative antimicrobials in patients with a history of penicillin allergy.^{34,52}

Cephalosporins and Allergy to Penicillins

Hypersensitivity is the most common adverse reaction to β -lactam antimicrobials. Allergic reactions were previously noted in 1% to 10% of patients treated with penicillins, making these antimicrobials the most allergenic of all drugs.⁵³ In reality, the overall cross-reactivity is approximately 1% when using first-generation cephalosporins or cephalosporins with similar R1 side chains as β -lactam antimicrobials due to improved manufacturing processes with less contamination. The use of third- or fourth-generation cephalosporins or cephalosporins with dissimilar side chains carries an almost negligible risk of cross allergy.^{34,55} Most often, the allergic response is a delayed reaction characterized by a maculopapular rash and/or fever. Less often but more serious is immediate hypersensitivity that is mediated by IgE antibodies. Manifestations of immediate hypersensitivity may include laryngeal edema, bronchospasm, and cardiovascular collapse. Allergic reactions may occur in the absence of previous known exposure to any of the penicillins. This may reflect prior unrecognized exposure to penicillin, presumably in ingested foods. Allergic reactions can occur with any dose or route of administration, although severe anaphylactic reactions are more often associated with parenteral than with oral administration. Some patients who experience cutaneous reactions may continue to receive the offending penicillin or receive the same penicillin in the future without experiencing a similar response.

The penicillin molecule itself is probably unable to form a complete antigen, but instead, the ring structure of penicillin is opened to form a hapten metabolite, penicilloyl. Approximately 95% of patients allergic to penicillin form this penicilloyl-protein conjugate (the major antigenic determinant); the remaining allergic patients form 6-aminopenicillic acid and benzylpenamalidic acid (minor antigenic determinants). Skin testing with a polyvalent skin test antigen, penicilloyl-polylysine, makes it possible to detect most patients who would develop a life-threatening allergic reaction if treated with a penicillin antimicrobial. Nevertheless, minor antigenic determinants that would not be detected by skin testing may produce severe allergic reactions.

Cross-reactivity

The presence of a common nucleus (β -lactam ring) in the structure of all penicillins means that allergy to one penicillin increases the likelihood of an allergic reaction to another penicillin. Furthermore, there would seem to be the potential for cross-reactivity between penicillins and cephalosporins as they both share a common β -lactam ring. However, actual cross-reactivity is rare.^{34,52}

Classification

Cephalosporins are classified as first-, second-, and third-generation because of their antimicrobial spectrum. In general, activity against gram-positive cocci decreases, and activity against gram-negative cocci increases from the first- to third-generation cephalosporins. First-generation cephalosporins are inexpensive, exhibit low toxicity, and are as active as second- and third-generation cephalosporins against staphylococci and nonenterococcal streptococci. For these reasons, first-generation cephalosporins have been commonly selected for antimicrobial prophylaxis in patients undergoing cardiovascular, orthopedic, biliary, pelvic, and intra-abdominal surgery (see “[Antimicrobial Prophylaxis for Surgical Procedures](#)” section). All cephalosporins can penetrate into joints and can readily cross the placenta.

First-Generation Cephalosporins

Cephalothin is the prototype of first-generation cephalosporins. Like most other cephalosporins, cephalothin is excreted largely unaltered by the kidneys, emphasizing the need to decrease the dose in the presence of renal dysfunction. Oral absorption is poor and IM injection is painful, accounting for its common administration by the IV route. Although cephalothin is present in many tissues and fluids, it does not enter the cerebrospinal fluid in significant amounts and is not recommended for treatment of meningitis. Cefazolin has essentially the same antimicrobial spectrum as cephalothin but has the advantage of achieving higher blood levels, presumably due to slower renal elimination. In this regard, cefazolin is viewed as the drug of choice for antimicrobial prophylaxis for many surgeries. This drug is well tolerated after IM or IV injection.

Second-Generation Cephalosporins

Cefoxitin and cefuroxime are examples of second-generation cephalosporins with extended activity against gram-negative bacteria. Cefoxitin is resistant to cephalosporinases produced by gram-negative bacteria. Cefuroxime is effective against *H influenzae* and is the only second-generation cephalosporin effective in the treatment of meningitis. Both drugs are excreted predominantly unchanged by the kidneys.

Third-Generation Cephalosporins

Third-generation cephalosporins have an enhanced ability to resist hydrolysis by the β -lactamases of many gram-negative bacilli including *E coli*, *Klebsiella*, *Proteus*, and *H influenzae*. Unlike older cephalosporins, the third-generation cephalosporins achieve therapeutic levels in the cerebrospinal fluid and can be used to treat meningitis. The third-generation cephalosporins seem to have the same relatively low toxicities as the older cephalosporins.

Cefotaxime was the first third-generation cephalosporin and has been effective in a broad range of infections, including meningitis caused by gram-negative bacilli other than *Pseudomonas*. The elimination half-time of this antimicrobial is approximately 1 hour, with clearance via the kidneys and hepatic metabolism. An adjustment in dosage or dosing interval is indicated in patients with renal dysfunction who are being treated with this drug. Approximately 30% of cefotaxime is excreted as a desacetyl derivative that has antibacterial activity and is synergistic with the parent compound. Ceftriaxone has the longest elimination half-time of any third-generation cephalosporin and is highly effective against gram-negative bacilli, especially *Neisseria* and *Haemophilus*. Cefixime is an orally effective third-generation cephalosporin that is as active as other cephalosporins against pneumococci, group A streptococci, and *H influenzae* but less active against *S aureus* and not active against anaerobes such as *Pseudomonas*. The spectrum of activity of cefixime and a single daily dose make it attractive for upper respiratory tract infections, but less expensive alternatives are available.

Fourth-Generation Cephalosporins

Fourth-generation cephalosporins are structurally related to the third-generation cephalosporins but possess an extra ammonium group that allows for enhanced activity against gram-negative bacteria. Cefepime is currently the only fourth-generation cephalosporin available in the United States. Its counterpart cefpirome is available overseas. Both have excellent activity against gram-positive bacteria such as methicillin-susceptible staphylococci and penicillin-resistant pneumococci. They are predominantly excreted unchanged in the urine.

Next (Fifth) Generation Cephalosporins

The fifth-generation cephalosporins such as ceftaroline and ceftobiprole are active against MRSA and gram-positive bacteria while retaining the activity of the later generation cephalosporins.

Other β -Lactam Antimicrobials

Aztreonam

Aztreonam is a monobactam antimicrobial that lacks the thiazolidine ring present in penicillins and the dihydrothiazine ring found in cephalosporins. The antimicrobial activity of this drug is limited to gram-negative bacteria. Aztreonam is not absorbed from the gastrointestinal tract, but therapeutic blood levels are achieved after IM or IV administration in most body tissues and fluids, including cerebrospinal fluid. The

elimination half-time is about 1.5 hours, and clearance is principally by glomerular filtration. Neither nephrotoxicity nor bleeding disorders have been reported. A unique advantage is the absence of any cross-reactivity between aztreonam and circulating antibodies of penicillin- or cephalosporin-allergic patients.⁵⁶ Because aztreonam combines the activity of the aminoglycosides with the low toxicity of the β -lactam antimicrobials, it can replace aminoglycosides in the treatment of many gram-negative infections. A potential disadvantage of aztreonam is the development of enterococcal superinfections. This antimicrobial is significantly more expensive than aminoglycosides.

Aminoglycoside Antimicrobials

Aminoglycosides are poorly lipid-soluble antimicrobials that are rapidly bactericidal for aerobic gram-negative bacteria. As would be predicted with the poor lipid solubility of these drugs, less than 1% of an orally administered aminoglycoside is absorbed into the systemic circulation. Aminoglycosides have a volume of distribution similar to the extracellular fluid volume and undergo extensive renal excretion due almost exclusively to glomerular filtration. There is a linear relationship between the plasma creatinine concentration and the elimination half-time of aminoglycosides. In the presence of normal renal function, the elimination half-time of aminoglycosides is 2 to 3 hours and is prolonged 20- to 40-fold in the presence of renal failure. Determination of the plasma concentration of aminoglycosides is an essential guide to the safe administration of these antimicrobials in the setting of renal dysfunction. The role of aminoglycosides is influenced by their toxicity (see “[Side Effects](#)” section) and cost-effectiveness relative to other antibiotics with broad gram-negative coverage.

Streptomycin was the first parenterally administered antimicrobial that was active against many gram-negative bacilli and *Mycobacterium tuberculosis*. Current use of this drug is limited because of the rapid emergence of resistant organisms, the frequent occurrence of vestibular damage during prolonged treatment, and the availability of less toxic antimicrobials.

Gentamicin is active against *P aeruginosa* as well as the gram-negative bacilli. Gentamicin penetrates pleural, ascitic, and synovial fluids in the presence of inflammation. Monitoring plasma concentrations of gentamicin is the best approach for recognizing potentially toxic levels ($>9 \mu\text{g/mL}$). If plasma concentrations of gentamicin cannot be monitored, the dose can be adjusted based on the plasma creatinine concentration.

Amikacin is a semisynthetic derivative of kanamycin that has the advantage of not being associated with the development of resistance. The principal use of amikacin is in the treatment of infections caused by gentamicin- or tobramycin-resistant gram-negative bacilli. Unlike other aminoglycosides, this drug should not be administered in combination with penicillin, which may result in antagonism of the bactericidal actions of penicillin against some strains of *Enterococcus faecalis*. The incidence of nephrotoxicity and ototoxicity is similar to that produced by gentamicin.

Neomycin is commonly used for topical application to treat infections of the skin (as after burn injury), cornea, and mucous membranes. Allergic reactions occur in 6% to 8% of patients treated with topical neomycin. Oral neomycin does not undergo systemic absorption and is thus administered to decrease bacterial flora in the intestine before gastrointestinal surgery and as an adjunct to the therapy of hepatic coma (decreases blood ammonia concentrations).

Side Effects

The side effects of aminoglycosides that limit their clinical usefulness include ototoxicity, nephrotoxicity, skeletal muscle weakness, and potentiation of nondepolarizing neuromuscular-blocking drugs. These side effects parallel the plasma concentration of the aminoglycoside, emphasizing the need to decrease the dose of these drugs in patients with renal dysfunction.

Ototoxicity

Ototoxicity manifests as vestibular dysfunction, auditory dysfunction, or both and parallels the accumulation of aminoglycosides in the perilymph of the inner ear. There is drug-induced destruction of vestibular or cochlear sensory hairs that is dose-dependent and most likely occurs with chronic therapy, especially in elderly patients, in whom renal dysfunction is more likely. Furosemide, mannitol, and probably other

diuretics seem to accentuate the ototoxic effects of aminoglycosides. Vestibular toxicity manifests as nystagmus, vertigo, nausea, and the acute onset of Ménière syndrome. Auditory dysfunction manifests as tinnitus or a sensation of pressure or fullness in the ears. Deafness may develop suddenly.

Nephrotoxicity

Aminoglycosides accumulate in the renal cortex and can produce acute tubular necrosis that initially manifests as an inability to concentrate urine and the appearance of proteinuria and red blood cell casts. These changes are usually reversible if the drug is discontinued. Neomycin is the most nephrotoxic of the aminoglycosides and therefore is not administered by the parenteral route.

Skeletal Muscle Weakness

Skeletal muscle weakness can occur with the intrapleural or intraperitoneal institution of large doses of aminoglycosides. This effect is most likely because of the ability of aminoglycosides to inhibit the prejunctional release of acetylcholine while also decreasing postsynaptic sensitivity to the neurotransmitter. An IV administration of calcium overcomes the effect of aminoglycosides at the neuromuscular junction. Patients with myasthenia gravis are uniquely susceptible to skeletal muscle weakness if treated with an aminoglycoside. Administration of a single dose of an aminoglycoside is unlikely to produce skeletal muscle weakness in an otherwise healthy patient.

Macrolides

Macrolides are stable in the presence of acidic gastric fluid, and as a result, these antimicrobials are well absorbed from the gastrointestinal tract. Structurally, these antimicrobials are characterized by 14 to 16 carbon atoms joined together in a complex, central molecule that is linked to various side chains.

Erythromycin

Erythromycin has a spectrum of activity, which includes most gram-positive bacteria, *Streptococcus pneumoniae*, *S aureus*, *Moraxella catarrhalis*, *H influenzae*, *Mycoplasma*, *Chlamydia pneumoniae*, and *Corynebacterium diphtheriae*. In patients who cannot tolerate penicillins or cephalosporins, erythromycin or clindamycin is an effective alternative for the treatment of streptococcal pharyngitis, bronchitis, and pneumonia. Unfortunately, *S aureus* is now developing that has increased resistance to clindamycin in both pediatric and adult populations.⁵⁷ Gastrointestinal intolerance is the most common side effect, which severely limits its use. The IV preparations are available for treatment of severe infections, but prolonged use by this route of administration is limited by the common occurrence of thrombophlebitis at the injection site and development of tinnitus or hearing loss in many patients. Severe nausea and vomiting may accompany infusion of erythromycin. Erythromycin is excreted largely in bile and only to a minor degree in urine. The dosage need not be altered in the presence of renal failure.

Effects on QTc

Oral erythromycin prolongs cardiac repolarization and is associated with reports of torsades de pointes.⁵⁸ Because erythromycin is extensively metabolized by cytochrome P-450 3A (CYP3A) isozymes, commonly used medications that inhibit the effects of CYP3A may increase plasma erythromycin concentrations thus increasing the risk of ventricular dysrhythmias and sudden death. The concurrent use of erythromycin and strong inhibitors of CYP3A such as ketoconazole is not recommended in mixed infection.

Azithromycin

Azithromycin resembles erythromycin in its antimicrobial spectrum, but an extraordinarily prolonged elimination half-time (68 hours) permits once-a-day dosing for 5 days (500 mg on day 1 and 250 mg on days 2-5). Tissue levels of azithromycin can be expected to remain at therapeutic levels for 4 to 7 days after a 5-day treatment course. Unlike clarithromycin, bioavailability of azithromycin is decreased by food such that the drug should be administered 1 hour before or 2 hours after meals.

Clindamycin

Clindamycin resembles erythromycin in antimicrobial activity, but it is more active against many anaerobes. Because severe pseudomembranous colitis can be a complication of clindamycin therapy, this drug should be used only to treat infections that cannot be adequately treated by less toxic antimicrobials. Significant diarrhea in patients treated with clindamycin is an indication to discontinue this drug and initiate evaluation for pseudomembranous colitis. However, clindamycin is indicated in the treatment of or prophylaxis for serious infections caused by susceptible anaerobes, particularly those originating in the gastrointestinal tract and female genital tract.

Only about 10% of administered clindamycin is excreted in an active form in urine; the remainder is changed into inactive metabolites. In patients with renal dysfunction, the elimination half-time of clindamycin is only slightly prolonged, and little change in dosage is required. In patients with severe liver disease, the dose of clindamycin may need to be decreased.

Side Effects

Clindamycin produces prejunctional and postjunctional effects at the neuromuscular junction, and these effects cannot be readily antagonized with calcium or anticholinesterase drugs. Large doses of clindamycin can induce profound and long-lasting neuromuscular blockade in the absence of nondepolarizing muscle relaxants and after full recovery from the effects of succinylcholine has occurred.⁵⁹ Skin rashes occur in about 10% of patients treated with clindamycin.

Vancomycin

Vancomycin is a bactericidal glycopeptide antimicrobial that impairs cell wall synthesis of gram-positive bacteria. The oral route of administration is used only for the treatment of staphylococcal enterocolitis and antimicrobial-associated pseudomembranous enterocolitis, taking advantage of the fact that vancomycin is poorly absorbed from the gastrointestinal tract. Vancomycin is administered IV for the treatment of severe staphylococcal infections or streptococcal or enterococcal endocarditis in patients who are allergic to penicillins or cephalosporins. Concomitant administration of an aminoglycoside is often necessary when vancomycin is used in the treatment of enterococcal endocarditis. Vancomycin is the drug of choice in the treatment of infections caused by MRSA. Vancomycin can be useful in the therapy of prosthetic heart valve endocarditis caused by *S epidermidis*. In this setting, vancomycin is often administered in combination with gentamicin or rifampin. Vancomycin is also used for prophylaxis against endocarditis in penicillin- and cephalosporin-allergic patients who have valvular heart disease and are undergoing dental procedures.

When vancomycin is administered IV, the recommendation is to infuse the calculated dose (10-15 mg/kg) over 60 minutes to minimize the occurrence of drug-induced histamine release and hypotension. As such, it can be begun 2 hours prior to surgery for prophylaxis. Infusion over 60 minutes produces sustained plasma concentrations for up to 12 hours. Vancomycin is principally excreted by the kidneys, with 90% of a dose being recovered unchanged in urine. The elimination half-time is approximately 6 hours and may be greatly prolonged (as long as 9 days) in the presence of renal failure. Determination of plasma vancomycin peak levels is an important guide to dosage (15-20 µg/mL is considered ideal) when this antimicrobial must be administered in the presence of renal dysfunction.⁶⁰

Side Effects

Rapid infusion (<30 minutes) of vancomycin has been associated with profound hypotension and even cardiac arrest.⁶¹⁻⁶⁴ Hypotension is often accompanied by signs of histamine release characterized by intense facial and truncal erythema (“red man syndrome”). The red man syndrome may occur even with slow infusion of vancomycin and is not always associated with hypotension.⁶⁵ Cardiovascular side effects most likely reflect nonimmunologic histamine release induced by vancomycin.⁶⁶ Although drug-induced histamine release initially causes increases in myocardial contractility, this effect is promptly followed by venodilation, a sudden decrease in left ventricular filling, and decreased contractility. Histamine produces hypotension in humans by directly dilating peripheral blood vessels. Direct myocardial depression produced by vancomycin manifesting as an unexpected decrease in heart rate does not seem to be important in causing hypotension in

humans.⁶⁶ Vancomycin may also produce allergic reactions characterized as anaphylactoid with associated hypotension, erythema, and occasionally bronchospasm.⁶⁴ Plasma tryptase concentrations are not increased following vancomycin-induced anaphylactoid reactions, thus permitting a method to distinguish anaphylactic from anaphylactoid reactions.⁶⁷ Arterial hypoxemia manifesting as an unexpected decrease in the oxygen saturation (SpO_2) may occur in association with vancomycin administration, perhaps reflecting drug-induced vasodilation in the lungs leading to an increase in ventilation to perfusion mismatching.⁶⁸ Oral H₁ (diphenhydramine 1 mg/kg) and H₂ (cimetidine 4 mg/kg) receptor antagonists administered 1 hour before induction of anesthesia decreased histamine-related side effects of rapid vancomycin infusion (1 g over 10 minutes).⁶⁹ In ambulatory anesthesia settings, as for orthopedic procedures, the time available for vancomycin administration before surgical incision or tourniquet inflation is often limited and may result in inadequate levels of antibiotic in blood and tissues if vancomycin cannot be administered more rapidly than 10 to 15 mg/kg over 60 minutes.

Ototoxicity is likely when persistent high plasma concentrations (>30 µg/mL) are present. The incidence of nephrotoxicity in association with vancomycin treatment is low. Particular attention to ototoxicity and nephrotoxicity is required when vancomycin is administered with an aminoglycoside. The administration of vancomycin to a patient recovering from succinylcholine-induced neuromuscular blockade has resulted in a return of neuromuscular blockade.⁷⁰

Linezolid

Linezolid, the first oxazolidinone antibiotic approved by the U.S. Food and Drug Administration, has a unique mechanism of action. It selectively binds to the 50S ribosomal unit and inhibits the synthesis of bacterial proteins. This unique mechanism prevents cross-resistance with other antibiotic agents.

Linezolid is used in the treatment of gram-positive bacteria such as skin and soft tissue infections caused by methicillin-sensitive and MRSA, vancomycin-resistant enterococci, hospital-acquired pneumonia caused by *S aureus*, and community-acquired pneumonia caused by *S pneumoniae*. Although the spectrum of activity is similar to vancomycin, linezolid has 100% oral bioavailability and lower incidences of red man syndrome, pruritus, and rash.^{71,72}

Side Effects

Linezolid appears to be relatively safe in short-term use. Nausea is typically the major side effect with case reports of hypoglycemia occurring within the first week of treatment. Long-term use, however, has been associated with bone marrow suppression, particularly thrombocytopenia, peripheral and ocular neuropathy, and lactic acidosis. Due to its nonspecific inhibition of monoamine oxidase, linezolid can cause serotonin toxicity when combined with serotonin reuptake inhibitors.⁷²

Bacitracins

Bacitracins are a group of polypeptide antibiotics effective against a variety of gram-positive bacteria. Use of these antimicrobials is limited to topical application in ophthalmologic and dermatologic ointments. Despite a perception that topical application of bacitracin rarely results in allergic reactions, there are reports of anaphylactic reactions following bacitracin nasal packing and mediastinal irrigation.^{73,74} Established topical uses of bacitracin include treatment of furunculosis, carbuncle, impetigo, suppurative conjunctivitis, and infected corneal ulcer.

Metronidazole

Metronidazole is bactericidal against most anaerobic gram-negative bacilli and *Clostridium* species. If administered orally, the drug is well absorbed and widely distributed in body tissues, including the CNS. As such, this antimicrobial has been useful in treating a variety of CNS, bone and joint infections, abdominal and pelvic sepsis, and endocarditis. In the past, orally administered metronidazole was used for treating pseudomembranous colitis secondary to *Clostridium difficile* infection (CDI). As of 2018, either vancomycin or fidaxomicin (a new macrocyclic antibiotic) is recommended over oral metronidazole for an initial episode

of CDI. In settings where access to vancomycin or fidaxomicin is limited, metronidazole may be used for an initial episode of nonsevere CDI.⁷⁵ An IV metronidazole is still a useful part of preoperative prophylactic regimens for elective colorectal surgery.

Side effects of metronidazole include dry mouth (metallic taste) and nausea. Concurrent ingestion of alcohol may cause a reaction similar to that produced when alcohol is ingested by patients taking disulfiram. Neuropathy and pancreatitis are infrequent.

Fluoroquinolones

The fluoroquinolones are broad-spectrum antimicrobials that are bactericidal against most enteric gram-negative bacilli and some gram-positive bacteria.⁷⁶ They are rapidly absorbed from the gastrointestinal tract, and penetration into body fluids and tissues is excellent. Their elimination half-time is prolonged (3-8 hours), and the principal route of excretion is via the kidneys, including glomerular filtration and renal tubular secretion. The dose of the fluoroquinolones should be decreased in the presence of renal dysfunction. Side effects are minimal, with mild gastrointestinal disturbances (nausea, vomiting) and CNS disturbances (dizziness, insomnia) occurring in less than 10% of treated patients. Fluoroquinolones have been useful clinically in the treatment of genitourinary and gastrointestinal infections, but soft tissue and bone infections have not responded to these drugs. Fluoroquinolones are bactericidal against most mycobacteria and are useful as part of multidrug regimens.^{77,78} Fluoroquinolones are associated with an increased risk of tendinitis and tendon rupture that is enhanced in patients older than 60 years of age, taking corticosteroid drugs, and in patients with kidney, heart, or lung transplants. In addition, fluoroquinolones may exacerbate muscle weakness in patients with myasthenia gravis.

Ciprofloxacin

Ciprofloxacin is highly effective in the treatment of urinary and genital tract infections, including prostatitis, and gastrointestinal infections. The major advantage of ciprofloxacin is its greatly enhanced serum concentration and its availability as an IV preparation. Because of high blood levels and good tissue penetration, ciprofloxacin has been useful in the treatment of a variety of systemic infections, including upper and lower respiratory tract infections, skin and soft tissue infections, and bone and joint infections. Most strains of *M tuberculosis* are susceptible to ciprofloxacin.

Moxifloxacin

Moxifloxacin is long acting for the treatment of acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, community-acquired pneumonia, skin infections, and complicated intra-abdominal infections. Because of serious adverse effects including peripheral neuropathy, syndrome of inappropriate secretion of antidiuretic hormone, tendonitis, acute liver failure, QTc prolongation, toxic epidermal necrolysis, psychotic reactions, and Stevens-Johnson syndrome, use is recommended only when less toxic options are not available.

Antiseptic and Disinfectant Prophylaxis for Surgical Procedures

Contamination of the surgical site is a requirement for surgical site infection. Decontamination of the skin with antiseptic preparations reduces the burden of skin flora and, in more recent randomized prospective studies, reduces the incidence of surgical site infection.⁷⁹ Centers for Disease Control and Prevention guidelines recommend showering or bathing with an antiseptic solution before surgery and the clinical practice guidelines from the National Institute for Health and Care Excellence recommend bathing or showering with soap, use of an iodine-impregnated drape, and immediate preparation with an antiseptic solution. Neither set of guidelines puts forth a preference of type of antiseptic solution. The main types of disinfectants are alcohols, chlorhexidine, and iodine-containing preparations, which can be used alone or in combination.

Topical Antiseptics

Alcohols

Alcohols are applied topically to decrease local cutaneous bacterial flora (quick drying and antisepsis) before penetration of the skin with needles. Their antiseptic action can be enhanced by prior mechanical cleansing of the skin with water and a detergent and gentle rubbing with sterile gauze during application.

Ethyl alcohol is an antiseptic of low potency but moderate efficacy, being bactericidal to many bacteria. On the skin, 70% ethyl alcohol kills nearly 90% of the cutaneous bacteria within 2 minutes, provided the area is kept moist. Greater than a 75% decrease in cutaneous bacterial count is unlikely with a single wipe of an ethyl alcohol-soaked sponge followed by evaporation of the residual solution. Isopropyl alcohol has a slightly greater bactericidal activity than ethyl alcohol. Alcohols reduce bacterial contamination and are not fungicidal or virucidal.

Fire Risks

It is important to recognize that alcohol-based preparations are flammable until all the liquid has evaporated.^{80,81} Alcohol-based surgical solutions can create a fire hazard (flash fire) especially if the solution is allowed to pool (eg, in the umbilicus) or the patient is draped before the solution is completely dry resulting in trapped alcohol vapors being channeled to the surgical site where a heat source may be used. Sterile towels may be used to absorb excess alcohol-based solutions. Safety checklists, sometimes called “Time Out” protocols, have been developed to assure compliance with preoperative preparation. The degree of fire hazard incurred due to skin preparation and the time required before surgical draping is often part of the protocol.

Coronavirus Disease 2019 Pandemic

During the coronavirus disease 2019 pandemic, alcohol-based hand rubs have been used to decrease contact transmission of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in hospitals. In suspension tests, SARS-CoV-2 was inactivated by ethyl alcohol and isopropyl alcohol at 30%, 40%, and 60% in 30 seconds.⁸² The SARS-CoV-2, in addition to other viruses such as Middle East respiratory syndrome coronavirus and endemic human coronaviruses, can persist on inanimate surfaces like metal, glass, or plastic for up to 9 days. However, these viruses can be inactivated by surface disinfectants including 62% to 71% ethanol, 0.5% hydrogen peroxide, and 0.1% sodium hypochlorite. Other biocidal agents such as 0.05% to 0.2% benzalkonium chloride and 0.02% chlorhexidine digluconate are less effective.⁸³

Chlorhexidine

Chlorhexidine is a colorless chlorophenol biguanide solution that disrupts cell membranes of the bacterial cells and is effective against both gram-positive and gram-negative bacteria. It persists on the skin to provide continued antibacterial protection. As a hand wash or surgical scrub, 2% chlorhexidine causes a greater initial decrease in the number of normal cutaneous bacteria than does povidone-iodine or hexachlorophene, and it has a persistent effect equal to or greater than that of hexachlorophene. Chlorhexidine is mainly used for the preoperative reduction of cutaneous flora for the surgeon and patient. It is also used to treat superficial infections caused by gram-positive bacteria and to disinfect wounds. As an antiseptic, chlorhexidine is rapid acting, has considerable residual adherence to the skin, has a low potential for producing contact sensitivity and photosensitivity, and is poorly absorbed even after many daily hand washings. Chlorhexidine solutions in an alcohol base are not appropriate for instillation into the eye (corneal injury) or middle ear (deafness).

Iodine

Iodine is a rapid-acting antiseptic that, in the absence of organic material, kills bacteria, viruses, and spores. For example, on the skin, 1% tincture of iodine will kill 90% of the bacteria in 90 seconds, whereas a 5% solution achieves this response in 60 seconds. In the presence of organic matter, some iodine is bound covalently, diminishing the immediate but not eventual effect. Nevertheless, commercial preparations contain iodine in such excess that minimal organic matter does not adversely influence immediate efficacy. The local toxicity of iodine is low, with cutaneous burns occurring only with concentrations of greater than 7%. In rare instances, an individual may be allergic to iodine and react to topical application. An allergic reaction usually manifests as fever and generalized skin eruption.

The most important use of iodine is disinfection of the skin. For this use, it is best used in the form of a tincture of iodine because the alcohol vehicle facilitates spreading and skin penetration. Iodine may also be used in the treatment of wounds and abrasions. Applied to abraded tissue, 0.5% to 1.0% iodine aqueous solutions are less irritating than the tinctures.

Iodophors

An iodophor is a loose complex of elemental iodine with an organic carrier that not only increases the solubility of iodine but also provides a reservoir for sustained release. The most widely used iodophor is povidone-iodine, in which the carrier molecule is polyvinylpyrrolidone. A 10% solution contains 1% available iodine, but the free iodine concentration is less than 1 ppm. This is sufficiently low that little, if any, staining of the skin occurs. Because of the low concentrations, the immediate bactericidal action is only moderate compared with that of iodine solutions.

Clinical Uses

The iodophors have a broad antimicrobial spectrum and are widely used as hand washes, including surgical scrubs; preparation of the skin before surgery or needle puncture; and treatment of minor cuts, abrasions, and burns. A standard surgical scrub with 10% povidone-iodine solutions (Betadine) will decrease the usual cutaneous bacterial population by greater than 90%, with a return to normal in about 6 to 8 hours. Compared with povidone-iodine, a disinfectant that contains an iodophor in isopropyl alcohol (DuraPrep) is more effective than povidone-iodine in decreasing the number of positive skin cultures immediately after disinfection as well as in bacterial regrowth and colonization of epidural catheters.

Corneal Toxicity

Chemical burns to the cornea may follow exposure (accidental splashes) to a variety of disinfectant solutions (chlorhexidine, hexachlorophene, iodine, alcohol, detergents containing iodine-based solutions). Povidone-iodine solution without detergent appears to be least toxic to the cornea, depending on concentration.⁸⁴

Preference for Chlorhexidine or Iodine for Skin Disinfection

Central vascular catheters are a common site of hospital-acquired infection. The superiority of chlorhexidine compared to iodine-based solutions has been examined in several studies. A meta-analysis of eight studies concluded that the incidence of bloodstream infections was significantly less when central vascular lines were inserted after skin preparation with chlorhexidine gluconate compared to povidone-iodine.⁸⁵ Similarly, chlorhexidine lowers the incidence of surgical site infections when used as a skin preparation prior to clean-contaminated abdominal surgeries as compared to povidone-iodine.^{86,87} In contrast, no difference was detected in catheter colonization when skin was prepared with iodine or chlorhexidine before epidural catheter insertion.⁸⁸ An iodophor in isopropyl alcohol solution was found to be superior to povidone-iodine, decreasing the number of positive skin cultures immediately after disinfection as well as in bacterial regrowth and colonization of epidural catheters⁸⁹ and chlorhexidine-impregnated split dressing may reduce colonization of epidural catheters.⁹⁰ However, concerns have been raised about potential neurotoxicity of chlorhexidine, which is inadvertently introduced into the neuraxial space.⁹¹

Quaternary Ammonium Compounds

Quaternary ammonium compounds are bactericidal in vitro to a wide variety of gram-positive and gram-negative bacteria. Many fungi and viruses are also susceptible. The *M tuberculosis*, however, is relatively resistant. Alcohol enhances the germicidal activity of quaternary ammonium compounds so that tinctures are more effective than aqueous solutions. The major site of action of quaternary ammonium compounds appears to be the cell membrane, where these solutions cause a change in permeability.

Benzalkonium and cetylpyridinium (mouthwash) are examples of quaternary ammonium compounds. These compounds may be used preoperatively to decrease the number of microorganisms on intact skin. There is a rapid onset of action, but the availability of more efficacious solutions has decreased their frequency of use. Quaternary ammonium compounds have been widely used for the sterilization of

instruments. Endoscopes and other instruments made of polyethylene or polypropylene, however, absorb quaternary ammonium compounds, which may decrease the concentration of the active ingredient to below a bactericidal concentration.

Hexachlorophene

Hexachlorophene (pHisoHex) is a polychlorinated bisphenol that exhibits bacteriostatic activity against gram-positive but not gram-negative organisms. Immediately after a hand scrub with hexachlorophene, the cutaneous bacterial population may be decreased by only 30% to 50% compared with greater than 90% following use of an iodophor. Nevertheless, 60 minutes later, the bacterial population surviving a hexachlorophene scrub will have decreased further to about 4%, whereas with the iodophor scrub, the bacterial population will have recovered to about 16% of normal.

Because most of the potentially pathogenic bacteria on the skin are gram-positive, 3% hexachlorophene is commonly used by physicians and nurses to decrease the spread of contaminants from caregivers' hands. This antiseptic is also used to cleanse the skin of patients scheduled for certain surgical procedures. Hexachlorophene may be absorbed through intact skin in sufficient amounts to produce neurotoxic effects, including cerebral irritability.

Methods for Sterilization of Instruments

The Centers for Disease Control and Prevention offer guidelines for disinfection and sterilization in health care facilities.⁹² Having a central processing department to ensure quality control is recommended; however, multiple methods are required throughout the hospital.

Formaldehyde

Formaldehyde is a volatile, wide-spectrum disinfectant that kills bacteria, fungi, and viruses by precipitating proteins. A 0.5% concentration requires 6 to 12 hours to kill bacteria and 2 to 4 days to kill spores. A 2% to 8% concentration is used to disinfect inanimate objects such as surgical instruments. Formaldehyde can be toxic, allergenic, and was named a known carcinogen by the U.S. National Toxicology Program in 2011. Most exposure is through volatilization and use under with fume hoods is recommended.

Glutaraldehyde

Glutaraldehyde is superior to formaldehyde as a disinfectant because it is rapidly effective against all microorganisms, including viruses and spores. This disinfectant also possesses tuberculocidal activity. Glutaraldehyde is less volatile than formaldehyde and hence causes minimal odor and irritant fumes. A period of 10 hours is necessary to sterilize dried spores, whereas an acid-stabilized solution kills dried spores in 20 minutes. Neither alkaline nor acidic solutions are damaging to most surgical instruments and endoscopes. As a sterilizing solution for endoscopes, glutaraldehyde is superior to iodophors and hexachlorophene.

Pasteurization

Pasteurization (hot water disinfection) is a process that destroys microorganisms in a liquid medium by application of heat. Pasteurizing water temperatures in the range of 55°C to 75°C will destroy all vegetative bacteria of significance in human disease as well as many fungi and viruses. Pasteurization kills bacteria by coagulating cell proteins, and water acts as a very effective medium for transferring the heat required to destroy organisms. This is the rationale for maximizing direct water contact with surfaces to be disinfected. Water temperatures of greater than 75°C may cause some plastic parts to deform. Equipment (respiratory therapy breathing circuits, anesthesia breathing circuits) should be submerged in water at 68°C for a minimum of 30 minutes. With respect to breathing circuits, pasteurization is effective against gram-negative rods, *M tuberculosis*, and most fungi and viruses. Pasteurization may be a cost-effective alternative to potentially toxic disinfecting solutions such as glutaraldehyde and formaldehyde.

Cresol

Cresol is bactericidal against common pathogenic organisms including *M tuberculosis*. It is widely used for disinfecting inanimate objects. Cresol should not be used to disinfect materials that can absorb this solution because burns could result from subsequent tissue contact.

Silver Nitrate

Silver nitrate is used as a caustic, antiseptic, and astringent. A solid form is used for cauterizing wounds and removing granulation tissue. It is conveniently dispensed in pencils that should be moistened before use. Solutions of silver nitrate are strongly bactericidal, especially for gonococci, accounting for its frequent use as prophylaxis for ophthalmia neonatorum.

Silver sulfadiazine or nitrate is used in the treatment of burns. With this use, hypochloremia may occur, reflecting the combination of silver ions with chloride. Hyponatremia also may result because the sodium ions are attracted by chloride ions into the exudate. Furthermore, absorbed nitrate can cause methemoglobinemia.

Ethylene Oxide

Ethylene oxide is a readily diffusible gas that is noncorrosive and antimicrobial to all organisms at room temperature. This gaseous alkylating material is widely used as an alternative to heat sterilization. It reacts with chloride and water to produce two additional active germicides, ethylene chlorohydrin and ethylene glycol. Special sterilizing chambers are required because the gas must remain in contact with the objects for several hours. Adequate airing of sterilized materials, such as tracheal tubes, is essential to ensure removal of residual ethylene oxide and thus minimize tissue irritation. Ethylene oxide sensitization has been described in children with spina bifida experiencing preoperative anaphylactic reactions, always in association with latex sensitization.⁹³

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Chemotherapeutic Drugs*

Updated by: Ami K. Patel • Richard D. Urman • James P. Rathmell

Chemotherapy is a term that was coined to refer to a broad range of chemicals (drugs) aimed at treating cancer by eradicating malignant cells anywhere in the body.¹ Conventional wisdom is that the effectiveness of chemotherapy requires that there be complete destruction (total cell kill) of all cancer cells because a single surviving cell with the ability to divide can give rise to sufficient progeny to ultimately kill the host. The role of the immune system in identifying and eliminating foreign tumor cells has gained increasing recognition, and harnessing our intrinsic immune surveillance system has become more and more a part of contemporary investigations of cancer and its treatment.² The use of several chemotherapeutic drugs (also called **antineoplastic drugs**) concurrently or in a planned sequence is commonly done in efforts to eradicate even small residual tumor cell populations that have survived treatment with a single or previous agent. In practice, combination chemotherapy regimens typically use the largest tolerated doses of each chemotherapeutic drug. Drugs that work via different mechanisms and that do not share similar toxic effects are often combined. Using a combination of agents that have different mechanisms also decreases the chances that drug-resistant tumor cell populations will emerge. Chemotherapeutic drugs used in combination are usually administered over short periods at specific treatment intervals rather than as continuous therapy. This approach is based on the empiric observation that normal cells usually recover more rapidly from a pulse of maximal chemotherapy than do malignant cells. Furthermore, immunosuppression is less profound with intermittent administration of chemotherapy. With rare exceptions, the optimal dose of chemotherapeutic drugs requires repetitive dosing because even if all cells in a tumor are sensitive to a drug, a single dose of the drug is not usually sufficient to kill the typically hundreds of millions of cells that are present in patients with cancer.

Malignant cells are often characterized by rapid division and synthesis of DNA. Most conventional chemotherapeutic drugs exert their antineoplastic effects on cells that are actively undergoing division (mitosis) or DNA synthesis. Many chemotherapeutic drugs act only at specific phases of the cell cycle (**Figure 42.1**).¹ The biology of the cancer being treated and the cell cycle specificity of agents affect how drugs are scheduled and combined for maximal effect. Slow-growing malignant cells with a slow rate of division, like carcinoma of the lung and colon, are often unresponsive or at best partially responsive to conventional chemotherapy. Conversely, rapidly dividing normal cells, like the cells found in the bone marrow, gastrointestinal mucosa, skin, and hair follicles, are more vulnerable to the toxic effects of chemotherapeutic drugs. Thus, it is predictable that clinical manifestations of toxicity caused by chemotherapeutic drugs often include myelosuppression (leukopenia, thrombocytopenia, or anemia), nausea, vomiting, diarrhea, mucosal ulceration, dermatitis, and alopecia because these represent activity at normal rapidly dividing cells. Myelosuppression is the dose-limiting factor for many chemotherapeutic drugs and is the most common toxicity that leads to temporary or permanent withdrawal of therapy. Drug-induced myelosuppression is usually reversible with discontinuation of the chemotherapeutic agent, supportive care with blood and platelet transfusions, and growth factor therapy as needed. Although rare, prolonged marrow failure may require intensive treatment with immunosuppression and consideration of bone marrow transplantation in certain instances.³

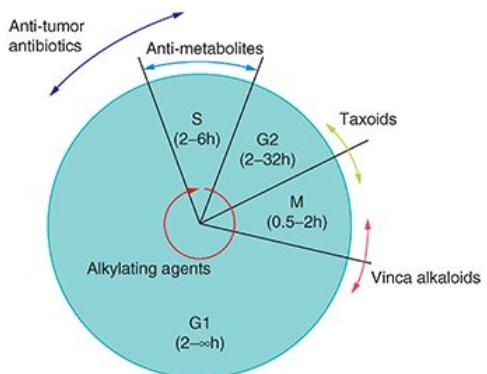


FIGURE 42.1 Cell cycle specificity of chemotherapy agents. The cell cycle is divided into a number of phases: G1 (gap 1; cells increase in size and prepare for DNA synthesis), S (synthesis; DNA replication occurs), G2 (gap 2; cells continue to grow and prepare for mitosis), and M (mitosis; cellular growth stops, and preparation for cell division takes place), each of which can vary in length according to the type of cell and the growth rate of the cell. The activity of different classes of certain chemotherapy agents (antibiotics, antimetabolites, taxoids, vinca alkaloids) is optimal in different phases of the cell cycle, whereas alkylating agents are relatively non–phase-specific. *Reprinted from Dickens E, Ahmed S. Principles of cancer treatment by chemotherapy. Surgery (Oxford). 2018;36(3):134-138. Copyright © 2017 Elsevier. With permission.*

Drug Resistance

Resistance to chemotherapeutic drugs often occurs and has many causes.⁴ Some chemotherapy agents lead to induction of drug-metabolizing enzymes in the liver, other tissues, or tumor cells, accelerating drug conversion to nontoxic metabolites. Many solid tumors grow so rapidly that portions of the tumor are poorly vascularized, preventing therapeutic concentrations from reaching many target cells. In poorly perfused areas of some tumors, cells remain resistant to chemotherapeutic drugs because of relative hypoxia. Indeed, hypoxia causes resistance to both radiation and most chemotherapeutic drugs (with the exception of malignancies susceptible to treatment with the mitomycins).

As in the treatment of infections, multiple drug resistance describes the clinical circumstance in which a tumor is no longer susceptible to several chemotherapeutic drugs. For a number of agents, P-glycoprotein spans the plasma membrane and acts to pump chemotherapeutic drugs (anthracyclines, vinca alkaloids, and taxanes but not alkylating drugs, platinating drugs, and antimetabolites) to the extracellular space such that an effective toxic intracellular concentration is not reached. In addition to P-glycoprotein, there is an additional family of multidrug resistance proteins that are located on plasma membranes and endoplasmic reticulum of some tumor cell types, which confer drug resistance via an adenosine triphosphate (ATP)-dependent decrease in cellular drug accumulation (with the exception of malignancies susceptible to treatment with the taxanes). Collectively, P-glycoprotein and the multidrug resistance proteins are members of the ATP-binding cassette (ABC) class of transporter proteins that protect normal tissues from a variety of toxicants and are overexpressed in some tumor cells. The breast cancer resistance protein (also known as the **ATP-binding cassette subfamily G member 2** or **ABCG₂ protein** or the **mitoxantrone resistance-associated protein**) is a specific example of an ABC protein that confers tumor resistance to certain chemotherapeutic agents via active transport of the offending agent out of cells expressing this transporter.

Topoisomerases, enzymes that regulate the overwinding or underwinding of DNA during replication, are the targets for many chemotherapeutic drugs. Resistance to chemotherapeutic drugs can also occur through mutations in the drug-binding domain of the target enzyme. Resistance to the drug methotrexate may reflect mutations in the drug target, the enzyme dihydrofolate reductase, resulting in its overexpression. Dihydrofolate reductase converts dihydrofolate into tetrahydrofolate and is required for the de novo synthesis of purines and thymidylic acid, which are important for cell growth and proliferation. Another potential mechanism of resistance includes decreased transport of methotrexate into the cell through the reduced folate

carrier. Resistance to alkylating drugs occurs through overexpression of drug-neutralizing substances and metabolizing proteins.

Classification

Chemotherapeutic drugs are classified according to their mechanism of action ([Table 42.1](#))¹; adverse effects associated with these drugs are generally similar among drugs with similar mechanisms of action ([Table](#)

[42.2](#)).^{5–7} Knowledge of drug-induced adverse effects and evaluation of appropriate laboratory tests (hemoglobin, platelet count, white blood cell count, coagulation profile, arterial blood gases, blood glucose, plasma electrolytes, liver and renal function tests, electrocardiogram [ECG], and radiograph of the chest) are useful in the preoperative evaluation of patients being treated with specific chemotherapeutic drugs.

Immunosuppression makes these patients susceptible to iatrogenic infections, making asepsis and the use of appropriate prophylactic antibiotics critical. A history of severe vomiting or diarrhea may be associated with electrolyte disturbances and decreased intravascular fluid volume. The existence of mucositis makes placement of pharyngeal airways, laryngeal mask airways, and esophageal catheters questionable. The response to inhaled and injected anesthetic drugs may be altered by drug-induced cardiac, hepatic, or renal dysfunction and induction of hepatic enzymes. The response to older nondepolarizing neuromuscular-blocking drugs may be altered by impaired renal function. Theoretically, the effects of succinylcholine may be prolonged if plasma cholinesterase activity is decreased by chemotherapeutic drugs. Additionally, many chemotherapeutic drugs are neurotoxic and result in chemotherapy-induced peripheral neuropathy (CIPN), which can profoundly affect the quality of life of patients. Prevention and pain management are therefore very important in preventing and managing CIPN as oncologic outcomes can be adversely affected by required dose modifications and/or premature discontinuation of chemotherapy secondary to CIPN. The incidence of CIPN is highest with use of platinum drugs, taxanes, vinca alkaloids, and bortezomib. It is often managed with duloxetine.

TABLE 42.1

Biochemical classification of chemotherapy drugs^a

Drug class	Mechanism of action	Examples
Alkylating agents	Impair cell function by forming covalent bonds on important molecules in proteins, DNA, and RNA; classified by their chemical structure and mechanism of covalent bonding	Cisplatin, carboplatin, chlorambucil, cyclophosphamide, ifosfamide
Antimetabolites	Structural analogues of naturally occurring metabolites involved in DNA and RNA synthesis. They either substitute for a metabolite that is normally incorporated into DNA or RNA or compete for the catalytic site of a key enzyme.	5-Fluorouracil, methotrexate, pemetrexed, mercaptopurine, gemcitabine
Antitumor antibiotics	Intercalate DNA at specific sequences, creating free radicals, which cause strand breakage. Anthracyclines are products of the fungus having <i>Streptomyces</i> ; also inhibit mechanism of action of topoisomerase I and II; required for the uncoiling of DNA during replication	Bleomycin, anthracyclines (doxorubicin, epirubicin)
Topoisomerase inhibitors	Topoisomerases are enzymes that control the 3-D structure of DNA. Topoisomerase I and topoisomerase II are enzymes responsible for the uncoiling of DNA during replication.	Topoisomerase I— irinotecan, topotecan Topoisomerase II— etoposide
Tubulin-binding drugs	Vinca alkaloids bind to tubulin and prevent the formation of the microtubule, which is important not only during mitosis but also for cell shape, intracellular transport, and axonal function.	Vinca alkaloids— vincristine, vinorelbine

	Taxoids prevent the disassembly of the microtubules, thereby inhibiting normal function.	Taxoids—docetaxel, paclitaxel
Signal transduction modifiers	Hormonal treatment of cancer results in a disruption of the normal growth factor receptor interactions, which lead to cell proliferation and is effective in cancer cells where mutations have resulted in uncontrolled cell proliferation utilizing activated signaling pathways. Monoclonal antibodies bind to specific antigens on tumor cells and thereby modify cell proliferation. Aromatase inhibitors work by inhibiting the action of the enzyme aromatase, which converts androgens into estrogens.	Antiestrogens— tamoxifen, toremifene, raloxifene Antiandrogens— flutamide, bicalutamide, nilutamide Monoclonal antibodies— rituximab, trastuzumab, etc Aromatase inhibitors — aminoglutethimide, anastrazole, letrozole Gonadotropin-releasing drugs— leuprolide, buserelin Progestins— megestrol acetate

^aModified from Dickens E, Ahmed S. Principles of cancer treatment by chemotherapy. *Surgery (Oxford)*. 2018;36(3):134-138. Copyright © 2017 Elsevier. With permission.

TABLE 42.2

Chemotherapeutic drugs, therapeutic uses, and associated side effects^a

Group and class	Therapeutic uses	Side effects (other than nausea and vomiting)
Alkylating agents		
Nitrogen mustards Mechlorethamine	Hodgkin disease Non-Hodgkin lymphoma	Myelosuppression Mucositis Alopecia
Cyclophosphamide	Acute lymphocytic leukemia Chronic lymphocytic leukemia Lymphomas Myeloma Neuroblastoma Breast, ovarian, cervical, and testicular cancer Lung cancer Wilms tumor Sarcoma	Myelosuppression Mucositis Alopecia Hemorrhagic cystitis Skin pigmentation Seizures Renal failure Cardiac failure Inappropriate secretion of vasopressin (ADH)
Melphalan	Myeloma Breast cancer	Myelosuppression
Chlorambucil	Hodgkin disease Non-Hodgkin lymphoma	Myelosuppression Secondary leukemias

Macroglobulinemia		
Ethyleneimine		
Hexamethylmelamine	Ovarian cancer	Myelosuppression Myelosuppression Alopecia Skin pigmentation Renal failure Mucositis Intracranial hemorrhage Seizure Hepatic dysfunction Cytomegalovirus infection Pneumonia
Thiotepa	Bladder, breast, and ovarian cancer	
Alkyl sulfonates		
Busulfan	Acute myelogenous leukemia Chronic myelogenous leukemia	Myelosuppression Thrombocytopenia
Nitrosoureas		
Carmustine (BCNU)	Hodgkin disease Non-Hodgkin lymphoma Astrocytoma Myeloma Melanoma	Myelosuppression Hepatitis Interstitial pulmonary fibrosis Renal failure Flushing
Lomustine (CCNU)	Hodgkin disease Non-Hodgkin lymphoma Astrocytoma Small cell lung cancer	Myelosuppression
Semustine (methyl-CCNU)	Colon cancer	Myelosuppression
Streptozotocin	Insulinoma Carcinoid tumor	Myelosuppression Hepatitis Renal failure
Triazenes		
Dacarbazine (DTIC)	Hodgkin disease Melanoma Sarcomas	Myelosuppression Flu-like syndrome
Temozolamide	Astrocytoma Melanoma	Hepatic toxicity Hyperglycemia Anemia Thrombocytopenia Lymphocytopenia
Bioreductive alkylating drugs		
Mitomycin-C	Head and neck, breast, lung, gastric, colon, rectal, and cervical cancer	Myelosuppression Mucositis Cardiac failure Interstitial fibrosis Hemolytic uremic syndrome
Platinum compounds		
Cisplatin	Head and neck, thyroid, lung, ovarian, endometrial, cervical, and testicular cancer	Myelosuppression Peripheral neuropathy Allergic reactions

	Neuroblastoma Osteogenic sarcoma	Renal toxicity Electrolyte abnormalities (hypocalcemia, hypomagnesemia, hypophosphatemia)
Carboplatin	As for cisplatin	Myelosuppression
Oxaliplatin	Colon cancer	Myelosuppression Peripheral neuropathy
Antimetabolites		
Folate analogues		
Methotrexate	Head and neck, breast, and lung cancer Acute lymphocytic leukemia Non-Hodgkin lymphoma Osteogenic sarcoma	Myelosuppression Mucositis Pneumonitis Hepatic fibrosis
Pyrimidine analogues		
Fluorouracil	Head and neck, breast, gastric, pancreatic, bladder, ovarian, cervical, and prostate cancer Hepatoma	Myelosuppression Mucositis Alopecia Pigmentation Chest pain
Cytarabine	Acute lymphocytic leukemia Acute myeloid leukemia Non-Hodgkin lymphoma	Myelosuppression Mucositis Hepatitis
Gemcitabine	Breast, lung, pancreatic, and bladder cancer	Myelosuppression Flu-like syndrome
Purine analogues		
Mercaptopurine	Acute lymphocytic leukemia Acute myeloid leukemia Chronic myeloid leukemia	Myelosuppression Anorexia Jaundice
Thioguanine	As for mercaptopurine	Myelosuppression Anorexia
Fludarabine	Chronic lymphocytic leukemia Non-Hodgkin lymphoma	Myelosuppression Optic neuritis Peripheral neuropathy Seizures Coma Depletion of CD4 cells
Pentostatin	Chronic lymphocytic leukemia Cutaneous T-cell lymphoma Hairy cell leukemia	Myelosuppression Depletion of T cells Hepatitis
Cladribine	Chronic lymphocytic leukemia Cutaneous T-cell lymphoma Hairy cell leukemia Waldenström macroglobulinemia	Myelosuppression Tumor lysis syndrome Asthenia
Hydroxyurea	Chronic myeloid leukemia Polycythemia vera Thrombocytopenia Melanoma	Myelosuppression Dermatologic changes
Topoisomerase inhibitors		

Anthracyclines		
Doxorubicin	Hodgkin disease Non-Hodgkin lymphoma Acute lymphocytic leukemia Neuroblastoma Thyroid, breast, lung, and gastric cancer	Myelosuppression Cardiomyopathy Mucositis
Daunorubicin	Acute myeloid leukemia Acute lymphocytic leukemia	
Idarubicin	As for daunorubicin	
Epirubicin	Hodgkin disease Non-Hodgkin lymphoma Acute lymphocytic leukemia Breast, lung, gastric, and bladder cancer	Myelosuppression Cardiomyopathy Alopecia Phlebitis
Anthracenediones		
Mitoxantrone	Acute myeloid leukemia Breast cancer	Myelosuppression Mucositis
Epipodophyllotoxins		
Etoposide	Hodgkin disease Non-Hodgkin lymphoma Acute myeloid leukemia Kaposi sarcoma Breast, lung, and testicular cancer	Myelosuppression Systemic hypotension Hepatitis Mucositis
Teniposide	Acute lymphocytic leukemia (children) Acute myeloid leukemia (children)	Myelosuppression Systemic hypotension
Dactinomycin	Wilms tumor Rhabdomyosarcoma Choriocarcinoma Kaposi sarcoma Ewing sarcoma Testicular cancer	Myelosuppression Mucositis Cheilitis Glossitis Alopecia Cutaneous erythema
Camptothecins		
Irinotecan	Colon cancer Ovarian cancer	Myelosuppression Alopecia
Topotecan	Lung cancer Ovarian cancer	As for irinotecan
Antitumor antibiotics		
Antibiotic		
Bleomycin	Hodgkin disease Non-Hodgkin lymphoma Head and neck cancer Testicular cancer	Interstitial pulmonary fibrosis Allergic reactions Skin pigmentation
Tubulin-binding drugs		
Vinca alkaloids		
Vinblastine	Hodgkin disease Non-Hodgkin lymphoma Breast cancer Testicular cancer	Myelosuppression Peripheral neuropathy

Vincristine	Hodgkin disease Non-Hodgkin lymphoma Small cell lung cancer Neuroblastoma Wilms tumor Rhabdomyosarcoma Acute lymphocytic leukemia	Myelosuppression Peripheral neuropathy
Vinorelbine	Breast cancer Lung cancer	Myelosuppression Peripheral neuropathy
Taxanes		
Paclitaxel	Breast, lung, bladder, and ovarian cancer	Myelosuppression Peripheral neuropathy Allergic reactions Alopecia totalis
Docetaxel	Breast, lung, bladder, and ovarian cancer	Myelosuppression Peripheral neuropathy Allergic reactions Alopecia totalis Cardiac dysrhythmias Capillary leakage
Signal transduction modulators		
Antiestrogens		
Tamoxifen	Breast cancer	Venous thrombosis Weight gain Amenorrhea Hypercalcemia Endometrial cancer Hot flashes
Toremifene	Breast cancer	Venous thrombosis Hot flashes
Raloxifene	Breast cancer	Venous thrombosis Hot flashes
Antiandrogens		
Flutamide	Prostate cancer	Gynecomastia Hot flashes
Bicalutamide	Prostate cancer	Gynecomastia Hot flashes
Nilutamide	Prostate cancer	Gynecomastia Hot flashes Delayed visual adaptation to dark
Monoclonal antibodies		
Trastuzumab	Breast cancer	Fever and chills Cardiomyopathy Rash Infusion reaction
Pertuzumab	Breast cancer	Fever and chills Cardiomyopathy Rash Infusion reaction

Bevacizumab	Cervical cancer Colorectal cancer Glioblastoma Hepatocellular cancer Non–small cell lung cancer Ovarian cancer Renal cell cancer	Hypertension Myelosuppression Postoperative wound complication Venous thromboembolism Gastrointestinal perforation Hemorrhage Non-GI fistulae development Congestive heart failure Posterior reversible encephalopathy syndrome (PRES)
Alemtuzumab	B-cell chronic lymphocytic leukemia	Myelosuppression Rash Fever Cytomegalovirus disease/viremia
Rituximab	Chronic lymphocytic leukemia Non-Hodgkin lymphoma	Infusion-related chills, rash, and fever Non-infusion-related myalgias, angioedema, bronchospasm, cardiac dysrhythmias Myelosuppression
Obinutuzumab	Chronic lymphocytic leukemia Follicular lymphoma	Infusion reaction Myelosuppression
Polatuzumab vedotin	Refractory diffuse large B-cell lymphoma	Infusion reaction Myelosuppression
Daratumumab	Multiple myeloma	Infusion reaction Myelosuppression
Other targeted therapies		
Imatinib	Philadelphia chromosome–positive CLL Philadelphia chromosome–positive ALL Gastrointestinal stromal tumors Myelodysplastic/myeloproliferative disease with PDGF receptor gene rearrangements	Peripheral edema Liver function abnormalities Rash Myelosuppression
Venetoclax	Chronic lymphocytic leukemia (CLL) Small lymphocytic lymphoma (SLL) Acute myelogenous leukemia (AML)	Tumor lysis syndrome Neutropenia
Sorafenib	Hepatocellular cancer Renal cell cancer Thyroid carcinoma	Diarrhea Hand-foot syndrome Stomatitis Cardiotoxicity
Sunitinib	Gastrointestinal stromal tumor Pancreatic neuroendocrine tumors Renal cell cancer	Diarrhea Hand-foot syndrome Stomatitis Myocardial infarction
Vaccines		
Sipuleucel-T	Prostate cancer	Severe infusion-related reaction

		Fevers Chills Fatigue Back pain Myalgias Citrate toxicity
Aromatase inhibitors		
Aminoglutethimide	Breast cancer	Orthostatic hypotension Glucocorticoid deficiency Cutaneous rash
Anastrazole	Breast cancer	Asthenia Headache Hot flashes
Letrozole	Breast cancer	Headache Heartburn
Gonadotropin-releasing drugs		
Leuprolide	Breast cancer Prostate cancer	Impotence Hot flashes Pain at sites of bony metastases (tumor flare)
Buserelin	Breast cancer	As for leuprolide
Progestin		
Megestrol acetate	Breast cancer Prostate cancer Endometrial cancer	Weight gain Peripheral edema Venous thromboembolism
Immunomodulatory drugs		
Thalidomide	Multiple myeloma	Somnolence Peripheral neuropathy Myelosuppression Venous thromboembolism Teratogenicity
Lenalidomide	Multiple myeloma	Somnolence Peripheral neuropathy Myelosuppression Venous thromboembolism Teratogenicity
Pomalidomide	Multiple myeloma	Somnolence Peripheral neuropathy Myelosuppression Venous thromboembolism Teratogenicity

Abbreviations: 3-D, three-dimensional; ADH, antidiuretic hormone; ALL, acute lymphoblastic leukemia; BCNU, bischloroethylnitrosourea; CCNU, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea; CLL, chronic lymphocytic leukemia; DTIC, dimethyl triazeno imidazole carboxamide; PDGF, platelet-derived growth factor.

^aAdapted from Rubin EH, Hait WN. Principles of cancer treatment. *Sci Am Med*. 2003;12(IV):1-17.

Toxicities

Chemotherapeutic drugs typically target proteins or nucleic acids, which are common to malignant and nonmalignant cells and thus possess a narrow therapeutic index. Therefore, using the standard definition of

therapeutic index (the dose that causes toxicity divided by the minimum effective dose) is not useful because these agents all produce significant, even life-threatening toxicities at doses, which may not reach levels that are high enough to eradicate cancer (therapeutic index <1). Furthermore, chemotherapeutic drugs are usually administered at maximum tolerated doses. Although toxicities may be unique for specific drugs, many toxicities are shared (nausea and vomiting, myelosuppression, mucositis, alopecia) (see [Table 42.2](#)).⁵ Nausea and vomiting result from local gastrointestinal effects as well as activation of the chemoreceptor trigger zone in the CNS. Patients who have a history of chemotherapy-induced nausea and vomiting are not necessarily prone to postoperative nausea and vomiting. Interestingly, there is only weak positive association between the two but patients who have a history of tolerating emetogenic chemotherapy regimens are unlikely to develop postoperative nausea and vomiting.⁸ Development of serotonin antagonists as effective antiemetics in addition to combination antiemetic regimens has facilitated the tolerance of emetogenic chemotherapeutic drugs. Mucositis and diarrhea are common gastrointestinal toxicities that reflect the high proliferative rate of gastrointestinal tissues, which makes these tissues more susceptible to the cytotoxic effects of certain chemotherapeutic drugs. Myelosuppression and alopecia reflect similar chemotherapeutic drug effects on highly proliferative tissues. Chemotherapeutic drugs that damage DNA (alkylating drugs, topoisomerases) are associated with secondary malignancies.

Alkylating Agents

Alkylating drugs include nitrogen mustards, alkyl sulfonates, nitrosoureas, and triazenes. These chemotherapeutic drugs form covalent alkyl bonds with nucleic acid bases, resulting in intrastrand or interstrand DNA cross-links, which are toxic to cells undergoing division. By altering the structure of DNA, these drugs inhibit DNA replication and transcription. The DNA damage produced by alkylating chemotherapeutic drugs is more likely to kill malignant cells than nonmalignant cells because rates of proliferation are greater for the cancer cells. Acquired resistance to alkylating drugs is a common occurrence and largely due to decreased cell membrane permeability to the drugs and increased production of nucleophilic substances that can compete with target DNA for alkylation.

Side Effects

Bone marrow suppression is the most important dose-limiting factor in the clinical use of alkylating drugs, especially busulfan. Cessation of mitosis is evident within 6 to 8 hours. Lymphocytopenia is usually present within 24 hours. Variable degrees of depression of platelet and erythrocyte counts may occur. Hemolytic anemia is predictably present.

Treatment with alkylating drugs is often associated with gonadal dysfunction, including oligospermia and amenorrhea. Hemorrhagic cystitis can result from irritation by the acrolein metabolite of cyclophosphamide or ifosfamide. Gastrointestinal mucosa is sensitive to the effects of alkylating drugs, manifesting as mitotic arrest, cellular hypertrophy, and desquamation of the epithelium. Damage to hair follicles, often leading to alopecia, is a common side effect. Increased skin pigmentation is frequent. All alkylating drugs are powerful central nervous system (CNS) stimulants, manifesting most often as nausea and vomiting. Skeletal muscle weakness and seizures may be present. Pneumonitis and pulmonary fibrosis are potential adverse effects of alkylating drugs. Symptomatic patients may demonstrate a decreased pulmonary diffusing capacity. Inhibition of plasma cholinesterase activity may be present for as long as 2 to 3 weeks after administration of chemotherapy regimens that include an alkylating agent and can lead to prolonged skeletal muscle paralysis after administration of succinylcholine.^{9,10}

Rapid drug-induced destruction of malignant cells can produce increased purine and pyrimidine breakdown, leading to uric acid-induced nephropathy. To minimize the likelihood of this complication, it is recommended that adequate fluid intake, alkalinization of the urine, and administration of allopurinol be established before drug treatment.

Nitrogen Mustards

The most commonly used nitrogen mustards are mechlorethamine, cyclophosphamide, melphalan, and chlorambucil.

Mechlorethamine

Mechlorethamine is a rapidly acting nitrogen mustard administered intravenously (IV) to minimize local tissue irritation. This drug must be freshly prepared before each administration. Mechlorethamine and other nitrogen mustards are intensely powerful vesicants, requiring that gloves be worn by personnel handling the drug. A course of therapy with mechlorethamine consists of the injection of a total dose of 6 mg/m^2 as a single dose on day 1 every 4 weeks for a total of two cycles for favorable/early-stage Hodgkin disease versus a total of three cycles for unfavorable/advanced stage Hodgkin disease. The drug undergoes rapid chemical transformation in tissues such that active drug is no longer present after a few minutes. For this reason, it is possible to prevent tissue toxicity from the drug by isolating the blood supply to that tissue. Alternatively, it is theoretically possible to localize the action of mechlorethamine in a specific tissue by injecting the drug into the arterial blood supply to the tissue.

Clinical Uses

Mechlorethamine produces beneficial effects in the treatment of Hodgkin disease and, less predictably, in other lymphomas. The drug is most often used in combination with vincristine (Oncovin), procarbazine, and prednisone (MOPP regimen) for the treatment of Hodgkin disease.

Side Effects

The major side effects of mechlorethamine include nausea, vomiting, and myelosuppression. Leukopenia and thrombocytopenia constitute the principal limitation on the amount of drug that can be given. Herpes zoster is a type of skin lesion frequently associated with nitrogen mustard therapy. Latent viral infections may be unmasked by treatment with mechlorethamine. Thrombophlebitis is a potential complication, and extravasation of the drug results in severe local tissue reactions, with brawny and tender induration that may persist for prolonged periods.

Cyclophosphamide

Cyclophosphamide is well absorbed after oral administration and is subsequently activated in the liver to aldophosphamide for transport to target tissues. Parenteral administration is also effective. Target cells are able to convert aldophosphamide to the highly cytotoxic metabolites, phosphoramide, and acrolein that then alkylate DNA. Maximal plasma concentrations of cyclophosphamide are achieved about 1 hour after oral administration, and the elimination half-life ranges from 3 to 12 hours. Urinary elimination accounts for approximately 15% to 25% of this drug in an unchanged form.

Clinical Uses

Cyclophosphamide is one of the most frequently used chemotherapeutic drugs because it is effective in the treatment of a wide range of cancers and inflammatory diseases. Its versatility is improved because of its effectiveness after oral as well as parenteral administration. Given in combination with other drugs, favorable responses have been shown in patients with Hodgkin disease, lymphosarcoma, Burkitt lymphoma, and acute lymphoblastic leukemia of childhood. In combination with doxorubicin and paclitaxel, cyclophosphamide is often used as neoadjuvant chemotherapy in the treatment of locally advanced breast cancer.

Cyclophosphamide is also used in combination with methotrexate and fluorouracil as adjuvant therapy after surgical resection of breast cancer when involvement of axillary lymph nodes is identified by pathology. This combination can also be used palliatively to treat heavily pretreated metastatic breast cancer.

Cyclophosphamide has potent immunosuppressive properties, leading to its use in nonneoplastic disorders associated with altered immune reactivity, including Wegener granulomatosis and rheumatoid arthritis.

Side Effects

Hypersensitivity reactions and fibrosing pneumonitis have been noted in patients treated with cyclophosphamide; the incidence is less than 1% and symptoms may develop months to years after initiation of the drug. Large doses of cyclophosphamide are associated with a high incidence of pericarditis and pericardial effusion, which in some cases progress to cardiac tamponade.¹¹ Smaller numbers of treated

patients develop hemorrhagic myocarditis with symptoms of congestive heart failure, which may not occur for as long as 2 weeks after the last dose of drug.

Cyclophosphamide differs from other nitrogen mustards in that significant degrees of thrombocytopenia are less common but alopecia is more frequent. Nausea and vomiting occur with equal frequency regardless of the route of administration. Mucosal ulcerations, increased skin pigmentation, and hepatotoxicity are possible side effects. Sterile hemorrhagic cystitis occurs in 5% to 10% of patients, presumably reflecting chemical irritation produced by reactive metabolites of cyclophosphamide. Dysuria and hematuria are indications to discontinue the drug. Inappropriate secretion of arginine vasopressin hormone has been observed in patients receiving cyclophosphamide, usually with doses of greater than 50 mg/kg. It is important to consider the possibility of water intoxication because these patients are usually being hydrated to minimize the likelihood that hemorrhagic cystitis will develop. Extravasation of the drug does not produce local reactions, and thrombophlebitis does not complicate IV administration.

Melphalan

Melphalan is a phenylalanine derivative of nitrogen mustard with a range of activity similar to other alkylating drugs. It is not a vesicant. Oral absorption is excellent, resulting in drug concentrations similar to those achieved by the IV route of administration. The elimination half-life is approximately 1.5 hours, and up to 10% of the drug is eliminated unchanged in urine.

Side Effects

The side effects of melphalan are primarily hematologic and are similar to those of other alkylating drugs. It is usually necessary to maintain a significant degree of bone marrow depression (leukocyte count 3,000-5,000 cells/mm³) to achieve optimal therapeutic effects. Pulmonary fibrosis is possible. Nausea and vomiting are not common side effects of melphalan. Alopecia does not occur, and changes in renal or hepatic function are possible.

Chlorambucil

Chlorambucil is the aromatic derivative of mechlorethamine. Oral absorption is adequate. The drug has an elimination half-life of approximately 1.5 hours and is almost completely metabolized. Chlorambucil is the slowest acting nitrogen mustard in clinical use. It is used to treat chronic lymphocytic leukemia and in primary (Waldenström) macroglobulinemia. A marked increase in the incidence of leukemia and other tumors has been noted with the use of this drug for the treatment of polycythemia vera.

Side Effects

Cytotoxic effects of chlorambucil on the bone marrow, lymphoid organs, and epithelial tissues are similar to those observed with other alkylating drugs. Its myelosuppressive action is usually moderate, gradual, and rapidly reversible. Pulmonary fibrosis is possible. Nausea and vomiting are frequent. A CNS stimulation can occur but has been observed only with large doses. Hepatotoxicity may rarely occur.

Alkyl Sulfonates

Busulfan is a cell cycle–nonspecific alkylating antineoplastic agent in the class of alkyl sulfonates. Busulfan is well absorbed after oral administration. Intravenous administration is also effective. Almost the entire drug is eliminated by the kidneys as methane sulfonic acid. Busulfan produces remissions in up to 90% of patients with chronic myelogenous leukemia. The drug is of no value in the treatment of acute leukemia.

Side Effects

Busulfan can produce progressive pulmonary fibrosis in up to 4% of patients. The prognosis after appearance of clinical symptoms is poor, with a median survival of 5 months.¹² Enhanced toxicity with administration of supplemental oxygen has not been noted. Myelosuppression and thrombocytopenia are important side effects of busulfan. Nausea, vomiting, and diarrhea occur. Hyperuricemia resulting from extensive purine catabolism

accompanying the rapid cellular destruction and renal damage from precipitation of urates have been noted. Allopurinol is recommended to minimize renal complications.

Nitrosoureas

The nitrosoureas are mustard gas-related compounds used as an alkylating agent in chemotherapy. Nitrosoureas, represented by carmustine, lomustine, semustine, and streptozocin, possess a wide spectrum of activity for human malignancies including intracranial tumors, melanomas, and gastrointestinal and hematologic malignancies. The high lipid solubility allows passage across the blood-brain barrier and therefore efficacy in the treatment of meningeal leukemias and brain tumors. These drugs act by carboxylation and alkylation of nucleic acids as well as cross-linking strands of DNA and RNA. With the exception of streptozocin, the clinical use of nitrosoureas is limited by profound drug-induced myelosuppression.

Carmustine

Carmustine is the nitrosourea in widest clinical use. It is capable of inhibiting synthesis of both RNA and DNA. Although oral absorption is rapid, the drug is injected intravenously because tissue uptake and metabolism occur quickly. Local burning may accompany infusion. Carmustine disappears from plasma in 5 to 15 minutes. Because of its ability to rapidly cross the blood-brain barrier, carmustine is used to treat meningeal leukemia and primary as well as metastatic brain tumors.

Side Effects

Carmustine has been associated with interstitial pneumonitis and fibrosis much like bleomycin.¹³ The incidence of pulmonary toxicity is in the range of 20% to 30%, with a mortality in those affected of 24% to 90%. The cumulative dose is the major risk factor, with 50% of patients exhibiting toxicity at doses above the range of 1,200 to 1,500 mg/m². A unique side effect of carmustine is a delayed onset (after approximately 6 weeks of treatment) of leukopenia and thrombocytopenia. Active metabolites may be responsible for this toxicity. The CNS toxicity, nausea and vomiting, flushing of the skin and conjunctiva, nephrotoxicity, and hepatotoxicity have been reported.

Lomustine and Semustine

Lomustine and its methylated analogue semustine possess similar clinical toxicity to carmustine, including delayed bone marrow suppression manifesting as leukopenia and thrombocytopenia. Lomustine appears to be more effective than carmustine in the treatment of Hodgkin disease.

Streptozocin

Streptozocin has a methylnitrosourea moiety attached to the number 2 carbon atom of glucose. It has a unique affinity for β cells of the islets of Langerhans and has proved useful in the treatment of human pancreatic islet cell carcinoma and malignant carcinoid. In animals, the drug is used to produce experimental diabetes mellitus.

Side Effects

Approximately 70% of patients receiving this drug develop hepatic or renal toxicity. Renal toxicity may manifest as tubular damage and progress to renal failure and death. Hyperglycemia can occur as a result of selective destruction of pancreatic β cells and resultant hypoinsulinism.¹⁴ Myelosuppression is not produced by this drug.

Mitomycin

Mitomycin is the prototypical alkylating agent and is of value in the palliative treatment of gastric adenocarcinoma in combination with fluorouracil and doxorubicin. The drug is administered IV and is widely distributed in tissues but does not readily enter the CNS. Metabolism is in the liver, with less than 10% of mitomycin excreted unchanged in bile or urine.

Side Effects

Myelosuppression is a prominent side effect of mitomycin and is characterized by severe leukopenia and thrombocytopenia, which may be delayed in appearance. Mitomycin is capable of inducing pulmonary fibrosis, with an incidence ranging between 3% and 12%.¹⁴ Like bleomycin, mitomycin appears to act synergistically to induce pulmonary fibrosis with thoracic radiation and oxygen therapy, suggesting the need to limit exposure of treated patients to hyperoxia. Nausea, vomiting, gastrointestinal mucositis, and alopecia are recognized toxic effects. Glomerular damage resulting in renal failure is a rare but well-recognized complication.

Platinating Drugs

Cisplatin

Although cisplatin is frequently designated as an alkylating agent, it has no alkyl group and cannot carry out alkylating reactions. It is correctly classified as alkylating-like. Cisplatin contains a platinum atom, two amines, and two chlorides, which result in chemotherapeutic effects resembling DNA alkylating drugs by cross-linking adjacent or opposing guanine bases to disrupt DNA. The drug must be administered IV because oral ingestion is ineffective. High concentrations of cisplatin are found in the kidneys, liver, intestines, and testes, but there is poor penetration into the CNS. Cisplatin and its analogue carboplatin are components of the treatment of many nonhematologic malignancies, including lung, bladder, testicular, and ovarian cancer.

Side Effects

Renal toxicity is prominent and becomes the dose-limiting toxic effect of cisplatin. Decreased glomerular filtration rate and renal tubular dysfunction produced by cisplatin may begin as early as 3 to 5 days after initiating treatment with this drug. Along with increasing blood urea nitrogen and plasma creatinine concentrations, proteinuria, and hyperuricemia, there is a magnesium-wasting defect in as many as 50% of patients manifesting as some degree of cisplatin-induced renal dysfunction. Acute tubular necrosis may progress to acute renal failure, necessitating hemodialysis. Hydration and diuresis induced with mannitol and furosemide may protect against the development of renal toxicity by dilution of the tubular urinary concentration of cisplatin. The hypomagnesemia that is associated with cisplatin's renal tubular injury may predispose to cardiac dysrhythmias and decrease the dose requirements for neuromuscular-blocking drugs.

Ototoxicity caused by cisplatin is manifested by tinnitus and hearing loss in the high-frequency range. Cisplatin is considered highly emetogenic, with marked nausea and vomiting occurring in almost all patients who do not receive antiemetics, although prophylactic antinausea regimens can be highly effective. Mild to moderate myelosuppression may develop, with transient leukopenia and thrombocytopenia. Peripheral sensory neuropathies, paresthesias, and loss of vibratory and position sense are common findings. Most neuropathies are reversible, although symptoms may persist for months. Hyperuricemia, seizures, and cardiac dysrhythmias have been observed. Allergic reactions characterized by facial edema, bronchoconstriction, tachycardia, and hypotension may occur minutes after injection of the drug.

Antimetabolites

Nucleic acid synthesis inhibitors (antimetabolites) include folate analogues, pyrimidine analogues, and purine analogues. These drugs are particularly effective in destroying cells during the S phase of the cell cycle, which is when DNA is synthesized. Selective effects on cancer cells are due to greater rates of DNA replication in cancer cells than normal cells. Nevertheless, side effects (myelosuppression and mucositis) reflect effects on proliferating but nonmalignant cells.

Folate Analogues

Methotrexate

Methotrexate is a poorly lipid-soluble folate analogue that is effective in the treatment of different hematologic and nonhematologic cancers and is classified as an antimetabolite (folic acid antagonist). This drug inhibits dihydrofolate reductase, which is the enzyme that uses reduced folate as a methyl donor in the

synthesis of pyrimidine and purine nucleosides. Inhibition of dihydrofolate reductase by methotrexate prevents the formation of tetrahydrofolic acid and causes disruption of cellular metabolism by producing an acute intracellular deficiency of folate enzymes. As a result, 1-carbon transfer reactions necessary for the eventual synthesis of DNA and RNA cease.

Methotrexate is readily absorbed after oral administration. Significant metabolism of methotrexate does not occur, with more than 50% of the drug appearing unchanged in urine. Renal excretion reflects glomerular filtration and tubular secretion. Toxic concentrations of methotrexate may occur in patients with renal insufficiency. Methotrexate remains in tissues for weeks, suggesting binding of the drug to dihydrofolate reductase.

Clinical Uses

Methotrexate is widely used in the treatment of malignant and some nonmalignant disorders. It is a useful drug in the treatment of acute lymphoblastic leukemia in children but not adults. Choriocarcinoma is effectively treated with this drug. Improvement in the clinical manifestations of psoriasis in patients reflects the effect of methotrexate on rapidly dividing epidermal cells characteristic of this disease. This drug may also be useful in the treatment of rheumatoid arthritis.

Methotrexate is poorly transported across the blood-brain barrier, and neoplastic cells that have entered the CNS probably are not affected by the usual plasma concentrations of the drug. Intrathecal injection is used to treat cerebral involvement with either leukemia, lymphoma, or choriocarcinoma.

Acquired resistance to methotrexate develops as a result of (1) impaired transport of methotrexate into cells, (2) production of altered forms of dihydrofolate reductase that have decreased affinity for the drug, and (3) increased concentrations of intracellular dihydrofolate reductase.

Side Effects

The most important side effects of methotrexate occur in the gastrointestinal tract and bone marrow. Leukopenia and thrombocytopenia reflect bone marrow depression. Ulcerative stomatitis and diarrhea are frequent side effects and require interruption of treatment. Hemorrhagic enteritis and death from intestinal perforation may occur. Pulmonary toxicity may take the form of fulminant noncardiogenic pulmonary edema, or a more progressive inflammation, with interstitial infiltrates and pleural effusions.¹⁵ The incidence of pulmonary toxicity attributed to methotrexate is in the range of 8%, but its frequent use in combination with other chemotherapeutic drugs makes this number uncertain.¹⁶ Methotrexate is associated with renal toxicity, with an incidence approaching 10% in higher doses.¹⁷ Renal insufficiency may be prevented by hydration and urinary alkalinization. Short-term or intermittent therapy with methotrexate results in increases in liver transaminase enzymes. Hepatic dysfunction is usually reversible but may sometimes lead to cirrhosis. It may be useful to measure liver function tests preoperatively in patients who have recently received methotrexate. Encephalopathic syndromes may accompany intrathecal or IV administration of methotrexate and may be transient or permanent.¹⁸ Additionally, alopecia and dermatitis are associated with administration of methotrexate. Folic acid antagonists also interfere with embryogenesis, emphasizing the risk in administering these drugs to pregnant patients. Normal cells can be protected from lethal damage by folate antagonists with sequential administration of folinic acid (leucovorin), thymidine, or both. This approach has been termed the **rescue technique**.

Pyrimidine Analogues

Pyrimidine analogues have in common the ability to prevent the biosynthesis of pyrimidine nucleotides or to mimic these natural metabolites to such an extent that they interfere with vital cellular activities such as the synthesis and functioning of nucleic acids. Examples of antimetabolite chemotherapeutic drugs that function as pyrimidine analogues are fluorouracil and cytarabine.

Fluorouracil

Fluorouracil blocks production of thymine nucleotides by inhibiting thymidylate synthase. This chemotherapeutic drug lacks significant inhibitory activity on cells and must be converted enzymatically to a

5'-monophosphate nucleotide. Administration of fluorouracil is usually by IV injection because absorption after oral ingestion is unpredictable and incomplete. Metabolic degradation occurs primarily in the liver, with an important metabolite being urea. Only approximately 5% to 20% of fluorouracil appears unchanged in urine. Fluorouracil readily enters the cerebrospinal fluid, with therapeutic concentrations being present within 30 minutes after IV administration.

Clinical Uses

Fluorouracil may be of palliative value in certain types of carcinoma, particularly of the breast and gastrointestinal tract. It can also be used as part of neoadjuvant or adjuvant chemotherapy regimens in the treatment of gastrointestinal malignancies and breast cancer. The drug is often used for the topical treatment of premalignant keratoses of the skin and superficial basal cell carcinomas.

Side Effects

Side effects caused by fluorouracil are difficult to anticipate because of their delayed appearance. Fluorouracil-induced myocardial ischemia is a rare cardiac toxicity that may lead to myocardial infarction up to 1 week after treatment.¹⁹ The incidence of this side effect is low in patients without underlying heart disease but may increase to 4.5% of treated patients with preexisting coronary artery disease. Stomatitis manifesting as a white patchy membrane that ulcerates and becomes necrotic is an early sign of toxicity and warns of the possibility that similar lesions may be developing in the esophagus and gastrointestinal tract. Myelosuppression, most frequently manifesting as leukopenia between 9 and 14 days of therapy, is a serious side effect. Thrombocytopenia and anemia may complicate treatment with fluorouracil. Loss of hair progressing to total alopecia, nail changes, dermatitis, and increased pigmentation and atrophy of the skin may occur. Hand-foot syndrome has also been associated with fluorouracil. Neurologic manifestations, including an acute cerebellar syndrome (ataxia), have been reported.

Capecitabine

Capecitabine is an orally administered drug that is metabolized to fluorouracil by thymidine phosphorylase after absorption from the gastrointestinal tract. Because there is more activity of thymidine phosphorylase in cancer cells (especially breast cancer) than in normal cells, capecitabine has the potential to be more selective than fluorouracil.

Pemetrexed

Pemetrexed is a folate antagonist that is effective in the treatment of mesothelioma and lung cancer. This drug inhibits multiple enzymes involved in the folate pathway, including thymidylate synthase and dihydrofolate reductase.

Cytarabine

Cytarabine (cytosine arabinoside), like other pyrimidine antimetabolites, must be activated by conversion to the 5'-monophosphate nucleotide before inhibition of DNA synthesis can occur. Both natural and acquired resistance to cytarabine develops, reflecting the activity of cytidine deaminase, an enzyme capable of converting cytarabine to the inactive metabolite arabinosyl uracil.

Clinical Uses

In addition to its chemotherapeutic activity, particularly in acute leukemia in children and adults, cytarabine has potent immunosuppressive properties. The drug is particularly useful in chemotherapy of acute granulocytic leukemia in adults. Intravenous administration of cytarabine is recommended because oral absorption is poor and unpredictable.

Side Effects

Cytarabine is a potent myelosuppressive drug capable of producing severe leukopenia, thrombocytopenia, and anemia. Cerebellar toxicity and ataxia can occur at high doses. Other side effects include gastrointestinal

disturbances, stomatitis, and hepatic dysfunction. Thrombophlebitis at the site of infusion is common. Alternatively, the drug may be given subcutaneously.

Gemcitabine

Gemcitabine resembles cytarabine structurally; yet, gemcitabine is active in several nonhematologic cancers, whereas cytarabine is not effective. Gemcitabine is also used in solid organ carcinomas, such as of the pancreas, breast, and lung. This most likely reflects unique effects of this chemotherapeutic drug on DNA and RNA metabolism. Common side effects associated with use of gemcitabine include bone marrow suppression, flu-like symptoms, fever, fatigue, mild nausea/vomiting, and diarrhea.

Purine Analogues

Antimetabolite chemotherapeutic drugs that function as purine analogues include mercaptopurine, azathioprine, thioguanine, pentostatin (2'-deoxycoformycin), and cladribine (2-chlorodeoxyadenosine). Mercaptopurine and thioguanine are analogues of the natural purines hypoxanthine and guanine, respectively.

Mercaptopurine

Mercaptopurine is incorporated into DNA or RNA strands and works by either blocking further strand synthesis or causes structural alterations that damage DNA. This drug is useful in the treatment of acute leukemia in children. Oral absorption is prompt, and gastrointestinal epithelium is not damaged. The elimination half-life is brief (about 90 minutes) due to rapid tissue uptake, renal excretion, and hepatic metabolism. One pathway of metabolism is methylation and subsequent oxidation of the methylated derivatives. A second pathway involves the enzyme xanthine oxidase, which oxidizes mercaptopurine to 6-thiouric acid. Allopurinol, as an inhibitor of xanthine oxidase, prevents conversion of mercaptopurine to 6-thiouric acid and thus increases the exposure of cells to mercaptopurine. The dose of mercaptopurine is decreased by about one-third when the drug is combined with allopurinol.

Side Effects

The principal side effect of mercaptopurine is a gradual development of bone marrow depression manifesting as thrombocytopenia, granulocytopenia, or anemia several weeks after initiation of therapy. Anorexia, nausea, and vomiting are common side effects; stomatitis and diarrhea rarely occur. Jaundice occurs in approximately one-third of patients and is associated with bile stasis and occasional hepatic necrosis. Hyperuricemia and hyperuricosuria may occur during treatment with mercaptopurine due to destruction of cells. This effect may require the use of allopurinol.

Thioguanine

Thioguanine is of particular value in the treatment of acute myelogenous leukemia, especially if given with cytarabine. After oral administration, thioguanine appears in the urine as a methylated metabolite and inorganic sulfate. Minimal amounts of 6-thiouric acid are formed, suggesting that deamination is not important in the metabolic inactivation of thioguanine. For this reason, thioguanine may be administered concurrently with allopurinol without a decrease in dosage, unlike mercaptopurine. Toxic manifestations of thioguanine treatment include bone marrow depression and, occasionally, gastrointestinal effects.

Pentostatin and Cladribine

Pentostatin and cladribine are purine analogues that have clinical activity against a variety of indolent lymphoid tumors, with the most dramatic effects occurring in patients with hairy cell leukemia.²⁰ These drugs act by irreversibly binding to adenosine deaminase (pentostatin) or by chemical modification of enzyme substrate, rendering it resistant to the action of adenosine deaminase (cladribine). Patients with acute leukemia and cells with high levels of adenosine deaminase activity are most likely to respond to these drugs. Fever, which is likely due to cytokines, is a side effect of treatment with cladribine. Both drugs are capable of producing immunosuppression. The recovery from immunosuppression seems to be more rapid after treatment with cladribine than after treatment with pentostatin, perhaps because of the shorter duration of

administration of the former. As a result, cladribine has emerged as the treatment of choice for hairy cell leukemia because of its minimal toxicity and its ability to induce a complete and sustained response with a single course of therapy.

Hydroxyurea

Hydroxyurea acts on the enzyme ribonucleoside diphosphate reductase to interfere with the synthesis of DNA. Oral absorption is excellent, and approximately 80% of the drug appears in the urine within 12 hours after oral or IV administration. The primary use of hydroxyurea is in the treatment of chronic myelogenous leukemia. It can also be used in the treatment of locally advanced squamous cell carcinomas of the head and neck excluding lip cancer in combination with chemoradiation.

Side Effects

Myelosuppression manifesting as leukopenia, megaloblastic anemia, and occasionally thrombocytopenia is the major side effect produced by hydroxyurea. Nausea and vomiting can also occur but are less frequent. Hyperpigmentation of the skin, stomatitis, and alopecia occur infrequently.

Topoisomerase Inhibitors

Topoisomerases are enzymes that correct alterations in DNA, which occur during replication and transcription. Certain chemotherapeutic drugs inhibit either topoisomerase I or topoisomerase II. Because cancer cells possess more topoisomerase activity than normal cells, there is more drug-induced DNA damage and resultant cell death. Toxicity reflects effects of inhibition of topoisomerase enzymes on normal proliferating tissues (myelosuppression, mucositis). Topoisomerase II inhibitors that include doxorubicin, daunorubicin, etoposide, and teniposide are part of most combination chemotherapy treatment regimens. Topoisomerase I inhibitors include topotecan and irinotecan. These drugs exhibit a broad spectrum of chemotherapeutic activity being useful in the treatment of leukemia and lung, colon, and ovarian cancer.

Doxorubicin and Daunorubicin

Doxorubicin and daunorubicin are anthracycline antibiotics that are natural products of certain soil fungi. Structurally, they contain a tetracycline ring attached to the sugar daunosamine by a glycosidic linkage. These drugs act by directly binding to DNA called *intercalation*, resulting in changes in the DNA helix that interfere with the ability of nucleic acids to serve as a template during replication in addition to disrupting DNA repair through topoisomerase II inhibition. These drugs also cause disruptive effects on cellular membranes. Drug-induced free radicals can overwhelm the heart's antioxidant defenses, leading to the oxidation of critical cardiac proteins and membrane components (unsaturated free fatty acids), leading to cardiotoxicity.²¹ Laboratory studies demonstrate that each subsequent dose of doxorubicin appears to diminish the heart's ability to withstand subsequent oxidant stress. Evidence also suggests that free radicals have a role in the protective effect of free radical scavengers.

Daunorubicin and doxorubicin are administered IV, with care taken to prevent extravasation because local vesicant action may result. There is rapid clearance from the plasma into the heart, kidneys, lungs, and liver. These drugs do not cross the blood-brain barrier to any significant extent. The urine may become red for 1 to 2 days after administration of these drugs.

Daunorubicin is metabolized primarily to deoxydaunorubicinol aglycone and daunorubicinol, whereas doxorubicin is excreted unchanged and as metabolites, including adriamycinol in the urine. Ultimately, approximately 40% of daunorubicin and doxorubicin are metabolized. Clinical toxicity may result in patients with hepatic dysfunction.

Clinical Uses

Daunorubicin is used primarily in the treatment of acute lymphocytic and myelocytic leukemia. Doxorubicin, which differs from daunorubicin only by a single hydroxyl group on the number 14 carbon atom, is also effective against a wide range of solid tumors. For example, doxorubicin is one of the most active single

drugs for treating many cancers including adenocarcinoma of the breast, carcinoma of the bladder, bronchogenic carcinoma, metastatic thyroid carcinoma, small cell carcinoma, and osteogenic carcinoma.

Resistance is observed to the anthracycline antibiotics, as with other chemotherapeutic drugs. Furthermore, cross-tolerance occurs between daunorubicin and doxorubicin. Cross-resistance also occurs between these antibiotics and the vinca alkaloids, suggesting that an alteration of cellular permeability is involved.

Side Effects

Cardiomyopathy and myelosuppression are side effects of the chemotherapeutic antibiotics. Leukopenia typically manifests during the second week of therapy. Thrombocytopenia and anemia occur but are usually less pronounced. Stomatitis, gastrointestinal disturbances, and alopecia are common side effects.

Cardiomyopathy

Cardiomyopathy is a unique dose related and often irreversible side effect of the anthracycline antibiotics. Increased plasma concentrations of troponin T reflect drug-induced injury to myocardial cells. Congestive heart failure develops in less than 3% of patients with a cumulative dose of doxorubicin of less than 400 mg/m², rising to 18% at 700 mg/m² (**Figure 42.2**).²² Prior mediastinal radiation or previous treatment with cyclophosphamide increases the subsequent risk of cardiomyopathy in response to administration of an anthracycline antibiotic. Marked impairment of left ventricular function for as long as 3 years after discontinuing doxorubicin has been observed. Previous treatment with anthracycline antibiotics may enhance myocardial depressant effects of anesthetic drugs even in patients with normal resting cardiac function.²³ Acute left ventricular failure 2 months after cessation of treatment with doxorubicin has been described during general anesthesia.²⁴

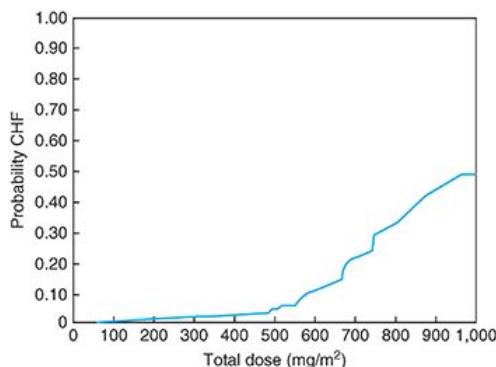


FIGURE 42.2 The probability of developing doxorubicin-induced congestive heart failure (CHF) versus the total cumulative dose of doxorubicin. *From Von Hoff DD, Layard MW, Basa P, et al. Risk factors for doxorubicin-induced congestive heart failure. Ann Intern Med. 1979;91(5):710-717. Copyright © 1979 American College of Physicians. All Rights Reserved. Reprinted with the permission of American College of Physicians, Inc.*

Two types of cardiomyopathies may occur.²¹ An acute form of cardiomyopathy occurs in approximately 10% of patients and is characterized by relatively benign changes on the ECG that include nonspecific ST-T changes and decreased QRS voltage. Other cardiac changes include premature ventricular contractions, supraventricular tachydysrhythmias, cardiac conduction abnormalities, and left axis deviation. These abnormalities occur during therapy at all dose levels and, except for decreased QRS voltage on the ECG, resolve 1 to 2 months after discontinuation of therapy. There is an associated acute reversible decrease in the ejection fraction within 24 hours after a single dose.

The second form of cardiomyopathy is characterized by the insidious onset of symptoms such as dry nonproductive cough, suggesting bronchitis, followed by rapidly progressive heart failure that is unresponsive to inotropic drugs and mechanical ventricular assistance.² This severe form of cardiomyopathy

occurs in almost 2% of treated patients and is fatal approximately 3 weeks after the onset of symptoms in nearly 60% of affected patients. Predictive tests to permit early recognition of impending cardiomyopathy are not available, although diminution in QRS voltage on the ECG is consistent with the diffuse character of the myocardial damage. Increased plasma concentrations of cardiac enzymes occur late in the course of cardiac failure and are of limited value in achieving an early diagnosis. Systolic time intervals and echocardiograms have been used to detect cardiotoxicity before the occurrence of clinically significant damage. Dexrazoxane is a free radical scavenger that protects the heart from doxorubicin-associated damage.²⁵

Dactinomycin

Dactinomycin (actinomycin D) is an antibiotic with chemotherapeutic activity resulting from its ability to bind to DNA, especially in rapidly proliferating cells. As a result of this binding, the function of RNA polymerase and thus the transcription of the DNA molecule are blocked. After IV injection, dactinomycin rapidly leaves the circulation. In animals, approximately 50% of an injected dose is excreted unchanged in bile and 10% in urine. Approximately 30% is excreted in the urine and feces within 1 week in humans. There is no evidence that the drug undergoes metabolism. Dactinomycin does not cross the blood–brain barrier in amounts sufficient to produce a pharmacologic effect.

Clinical Uses

The most important clinical use of dactinomycin is the treatment of Wilms tumor in children, rhabdomyosarcoma, and Ewing sarcoma. It may be effective in some women with methotrexate-resistant gestational trophoblastic neoplasia. Occasionally, this drug is used to inhibit immunologic responses associated with organ transplantation.

Side Effects

The toxic effects of dactinomycin include the early onset of nausea and vomiting, often followed by myelosuppression manifesting as pancytopenia 1 to 7 days after completion of therapy. Pancytopenia may be preceded by thrombocytopenia as the first manifestation of bone marrow suppression. Glossitis, ulcerations of the oral mucosa, diarrhea, alopecia, and cutaneous erythema are commonly associated with dactinomycin therapy. Extravasation of the drug results in tissue necrosis.

Bleomycin

Bleomycins are water-soluble glycopeptides that differ from one another (there are more than 200 congeners) in their terminal amine moiety. The terminal amine is coupled through an amide linkage to a carboxylic acid. Bleomycin possesses a tripeptide component that binds DNA and a metal-binding region. In the presence of oxygen and either iron or copper, bleomycin produces free radicals, which create DNA breaks.

Bleomycin is administered IV, and high concentrations occur in the skin and lungs. The drug accumulates in tumors, suggesting the presence of a lower level of inactivating enzyme. Bleomycin is eliminated primarily by renal excretion, with approximately 50% of the dose cleared within 4 hours and 70% by 24 hours.²⁶ Therefore, excessive concentrations of drug occur if usual doses are administered to patients with impaired renal function.

Clinical Uses

Bleomycin is effective in the treatment of testicular carcinoma, particularly if administered in combination with vinblastine, as well as Hodgkin lymphoma. It can also be used to treat squamous cell carcinomas of the head, neck, esophagus, skin, and genitourinary tract with palliative intent.

Side Effects

The most common side effects of bleomycin are mucocutaneous reactions including stomatitis, alopecia, pruritus, erythema, and hyperpigmentation, which occur in approximately 45% of patients. In contrast to other chemotherapeutic drugs, bleomycin causes minimal myelosuppression. Unexplained exacerbations of rheumatoid arthritis have occurred.

Patients with lymphomas who are receiving bleomycin may develop an acute reaction characterized by hyperthermia, hypotension, and hypoventilation. The likely mechanism is the release of an endogenous pyrogen, presumably from destroyed tumor cells. An initial small test dose of bleomycin is recommended to minimize the occurrence of this syndrome.

Pulmonary Toxicity

The most serious side effect of bleomycin is dose-related pulmonary toxicity ([Figure 42.3](#)).¹² Indeed, bleomycin is concentrated preferentially in the lungs and is inactivated by a hydrolase enzyme, which is relatively deficient in lung tissue. Initially, bleomycin produces pulmonary capillary endothelial damage, progressing to alveolar epithelial injury with necrosis of type 1 and proliferation of type 2 alveolar cells. Interstitial fibrosis develops and may progress to involve the entire lung. It is estimated that some form of pulmonary toxicity (most often pulmonary fibrosis) occurs in 4% of patients treated with bleomycin. Fatal pulmonary toxicity has occurred with bleomycin doses as low as 100 mg but more often in the presence of other risk factors ([Table 42.3](#)).

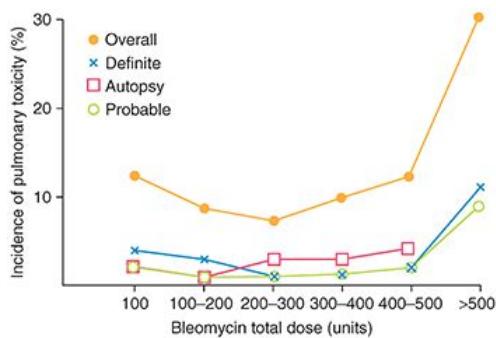


FIGURE 42.3 The relationship between the total dose of bleomycin and the incidence of pulmonary toxicity. *Reprinted from Ginsberg SJ, Comis RL. The pulmonary toxicity of antineoplastic agents. Semin Oncol. 1982;9(1):34-51. Copyright © 1982 Elsevier. With permission.*

TABLE 42.3

Risk factors for development of chemotherapy-induced pulmonary toxicity

Total drug dose

Age

Concurrent or prior chest radiation

Oxygen therapy

Combination chemotherapy

Preexisting pulmonary disease

Genetic predisposition

Cigarette smoking

The first signs of pulmonary toxicity are cough, dyspnea, and basilar rales, which progress in one of two directions. A mild form of pulmonary toxicity is characterized by exertional dyspnea and a normal resting PaO_2 . A more severe form of arterial hypoxemia at rest is associated with radiographic findings of interstitial pneumonitis and fibrosis. Lesions are found more frequently in lower lobes and subpleural areas, and radiographs of the chest often reveal basilar and perihilar infiltrates. The alveolar-arterial gradient for oxygen is increased, and pulmonary diffusion capacity may be decreased. Pulmonary function studies have been of no greater value than clinical signs in detecting the onset of pulmonary toxicity.

Early reports of postoperative respiratory failure in bleomycin-treated patients suggested that either arterial hyperoxia or excessive crystalloid administration played a role in the exacerbation of pulmonary

fibrosis.^{27–29} One speculation is that acutely increased inhaled concentrations of oxygen facilitate production of superoxide and other free radicals in the presence of bleomycin. For this reason, it has been recommended that inhaled oxygen concentrations be maintained below 30% in bleomycin-treated patients. Animal model literature confirms that the continuous administration of inspired oxygen concentrations of greater than 30% immediately after exposure to bleomycin increases pulmonary damage.³⁰ Nevertheless, it is unlikely that patients will present to the operating room immediately after treatment with bleomycin. A more practical question is whether hyperoxia for short periods of time several days after treatment is a risk factor for bleomycin-induced pulmonary damage.³¹ In this regard, animal studies have confirmed that delayed exposure to supplemental oxygen after bleomycin treatment is not harmful.³² Nevertheless, there are case reports of respiratory failure with inspired oxygen concentrations greater than 30% in patients last exposed to bleomycin up to 6 to 12 months before hyperoxia. Patients with prior exposure to bleomycin but with no risk factors appear to be at a minimum risk from hyperoxia. In contrast, those patients with one or more major risk factors (preexisting pulmonary damage from bleomycin, which is more likely if the total dose is >450 mg; renal dysfunction, which slows clearance of the drug from the lungs; and/or prior exposure to bleomycin within a 1- to 2-month period) may be at higher risk for the development of bleomycin-induced hyperoxic pulmonary injury in the operating room. It may be prudent to maintain these patients on the minimum inspired oxygen concentration that can be used safely intraoperatively to provide oxygen saturations of greater than 90% by pulse oximetry.³¹ The value of corticosteroids as pretreatment in patients with risk factors and in whom greater than 30% oxygen may be needed; for example, operations requiring cardiopulmonary bypass, has not been confirmed by controlled studies. The role of excessive crystalloid administration has not received the same scrutiny as increased delivered oxygen concentrations. A consideration in this regard is replacement of fluids with colloids rather than crystalloids to decrease or prevent pulmonary interstitial edema in bleomycin-treated patients undergoing surgery. Accumulation of interstitial fluid may reflect impaired lymphatic function caused by bleomycin-induced fibrotic changes in the lungs. In the future, bleomycin may be replaced with phleomycin, an analogue of bleomycin that has lower pulmonary toxicity and a broader effectiveness against multiple types of tumors.³³

Tubulin-Binding Drugs

Microtubules are subcellular structures that are essential for normal function of cells. They form the architecture to maintain cell shape, organize the location of organelles, and mediate intracellular transport and secretion, neurotransmission, axonemal flow, and cell motility.³⁴ Vinca alkaloids and taxanes are examples of antimitotic chemotherapeutic drugs that disrupt the normal function of microtubules. Vinca alkaloids bind to depolymerized microtubules and inhibit microtubule formation. Taxanes bind to polymerized microtubules and inhibit their breakdown. The result of these interactions is the failure of the cell to undergo normal mitosis leading to cell death.

Vinca Alkaloids

Vinca alkaloids represent the active medicinal ingredients from the pink periwinkle plant and include vincristine, vinblastine, vinorelbine, and vindesine. Vincristine is highly effective against Hodgkin disease, non-Hodgkin lymphoma, and pediatric solid tumors; yet, it has little activity against adult solid tumors. Vinorelbine, in contrast, is active against breast and lung cancer. Vinblastine is most often used in the treatment of testicular cancer and non-Hodgkin lymphoma.

Side Effects

Myelosuppression manifesting as leukopenia, thrombocytopenia, and anemia are the most prominent side effects of vinca alkaloids, appearing 7 to 10 days after initiation of treatment. Vincristine is less likely than vinblastine and vinorelbine to cause bone marrow depression.

Symmetric peripheral sensory-motor neuropathy often occurs during administration of therapeutic doses of vincristine and may become the dose-limiting side effect.^{35,36} Clinical manifestations may include several aspects of peripheral nerve function with areflexia (loss of Achilles tendon reflex) being the earliest finding. Paresthesias in the hands and feet, weakness and atrophy of the extremities, and skeletal muscle pain make

use of the hands and feet difficult (ataxia). Tremors frequently develop, whereas neuropathic pain and foot drop are common. Autonomic neuropathy with orthostatic hypotension, bowel motility dysfunction, and cranial nerve involvement (laryngeal nerve paralysis with hoarseness, weakness of the extraocular muscles) are present in about 10% of treated patients.³⁷ The CNS effects (confusion, insomnia, seizures, hallucinations) due to vincristine are rare, presumably because of poor penetration of the blood–brain barrier by the drug. The peripheral neuropathy is mainly axonal, but demyelination may also occur as demonstrated by measurement of somatosensory evoked potentials.³⁶ Vincristine-induced peripheral neuropathy is said to be reversible after discontinuing the drug, although this may require months, and in some patients, the resolution may be incomplete.³⁵ There is limited evidence that suggests that neuraxial anesthesia and peripheral nerve blocks can be safely and effectively used in patients with preexisting peripheral neuropathy without significant risk of worsening of the neuropathy. The concentration of local anesthetic should be reduced, epinephrine should be avoided, and a nerve localization technique that minimizes the likelihood of intraneuronal injection should be used in efforts to minimize the risk of worsening the neuropathy.³⁸ Neuropathies do worsen during the perioperative period in a small number of patients whether general or regional anesthesia is used. Thus, a careful risk-benefit assessment and informed decision making along with each individual patient is essential.

The syndrome of hyponatremia associated with high urinary sodium and inappropriate secretion of arginine vasopressin hormone has occasionally been observed during vincristine therapy. An effect on the autonomic nervous system can cause paralytic ileus and abdominal pain, which commonly develops during vinblastine therapy. Urinary retention, tenderness of the parotid glands, dryness of the mouth, and sinus tachycardia are other occasionally experienced manifestations of altered autonomic nervous system activity. Transient mental depression is most likely to occur on the second or third day of treatment with vinblastine. Alopecia appears to occur more frequently with vincristine than with vinblastine. Vinorelbine may cause chest pain, bronchospasm, dyspnea, and pulmonary infiltrations.

Taxanes

Paclitaxel (active extract from the Pacific yew tree) and docetaxel (more water-soluble semisynthetic derivative) share a broad spectrum of similar chemotherapeutic activity against breast, lung, ovarian, and bladder cancer.³⁹ Both drugs are also active against lymphoid malignancies. Taxanes block the function of the mitotic apparatus by impeding the normal function of microtubules. Unlike vinca alkaloids, which affect the rates of tubulin polymerization, the taxanes inhibit microtubule depolymerization in a dose-dependent manner. The microtubules formed in the presence of taxanes are extraordinarily stable and dysfunctional, thereby causing the death of the cell by disrupting the normal microtubule dynamics required for cell division.

Taxanes are rapidly cleared from the plasma despite extensive binding to proteins. The volume of distribution is large, suggesting binding to cellular proteins, possibly tubulin. Renal clearance accounts for a small proportion (<10%) of total clearance. Hepatic metabolism, biliary excretion, fecal elimination, or extensive tissue binding appears to be responsible for most of the plasma clearance.

Side Effects

Taxanes are associated with myelosuppression, peripheral neuropathy, and alopecia. Severe neurotoxicity precludes the administration of high doses of taxanes. The peripheral neuropathy is characterized by sensory symptoms such as numbness and paresthesia in a glove-and-stockinet distribution. Patients may also experience transient taxane-associated arthralgias and myalgias for several days following treatment. Cardiac effects, including dysrhythmias, myocardial ischemia, and transient asymptomatic bradycardia may be more common with paclitaxel than docetaxel. Docetaxel seems to have unique vascular permeability properties, which may result in peripheral edema, pleural effusion, and ascites. Fluid retention produced by docetaxel is dose-dependent and may be decreased by pretreatment with dexamethasone. Docetaxel also produces skin toxicities including an erythematous maculopapular rash on the forearms and hands. Hypersensitivity reactions (flushing, bronchospasm, dyspnea, systemic hypotension) caused by direct release of histamine or other chemical mediators may occur in 25% to 30% of patients treated with taxanes.³⁹

Estramustine

Estramustine exerts its chemotherapeutic effects by inhibition of microtubule assembly and depolymerization. This drug also binds to an estramustine-binding protein in prostate tissue explaining the possible usefulness of this drug as part of combination therapy of hormone-refractory prostate cancer. Although it increased the prostate-specific antigen response rate in these patients, it did not improve overall survival or grade 3 or 4 toxicity.⁴⁰

Signal Transduction Modulators

Signal transduction modulators (hormones) that may be useful in the treatment of neoplastic disease include antiestrogens, antiandrogens, aromatase inhibitors, gonadotropin-releasing drugs, and progestin. Normal cell division results from the interaction of growth factors with specific receptors. This interaction initiates a series of enzyme reactions (signal transduction), culminating in activation of nuclear transcription factors that produce cell proliferation molecules. Mutations in cancer cells result in uncontrolled cell proliferation using activated signaling pathways. Hormonal treatment of cancer disrupts growth factor receptor interactions.

Progestins

Progestational drugs are useful in the management of patients with endometrial carcinoma. Progestins act by reducing the production of hormones that stimulate the neoplastic endometrium.

Estrogens and Androgens

Malignant changes in the breast and prostate often depend on hormones for their continued growth. For example, prostatic cancer is stimulated by androgens, whereas orchectomy or estrogens (diethylstilbestrol) slow the growth of the tumor cells. Eventually, prostatic tumors become insensitive to the lack of androgen or the presence of estrogens, presumably because of the survival of progressively undifferentiated cells that favor the emergence of cell types that no longer depend on androgens for their growth.

Malignant tissues that are responsive to estrogens contain receptors for the hormone, whereas malignant tissues lacking these receptors are unlikely to respond to hormonal manipulation. The onset of action of hormone therapy is slow, requiring 8 to 12 weeks.

Hypercalcemia may be associated with androgen or estrogen therapy, requiring adequate hydration in an attempt to facilitate renal excretion of calcium. Plasma calcium concentrations should be determined in patients receiving treatment with these hormones.

Antiestrogens

Antiestrogens, such as tamoxifen, are useful in the treatment of breast cancer that expresses estrogen or progesterone receptors. The estrogen receptor resides in the cytosol and, upon occupation by estradiol, is transported to the nucleus, where it activates genes (including those genes that encode proliferation molecules) containing estrogen-response elements. Tamoxifen binds to estrogen receptors and disrupts receptor interactions with estrogen in some but not all estrogen-responsive tissues. For example, tamoxifen is antiestrogenic in breast and ovarian tissue but is estrogenic in the uterus, liver, and bone. As a result, tamoxifen is effective in the prevention and treatment of breast cancer but produces undesired estrogen side effects including deep vein thrombosis (<1% of patients), endometrial cancer (about 0.3% of patients), and early menopausal symptoms (hot flashes). In addition, tamoxifen lowers plasma cholesterol concentrations and increases bone density.

The response to tamoxifen is proportional to the degree of expression of estrogen receptors in breast tumors. Tamoxifen is of little benefit in women with breast cancer that does not express hormone receptors. After surgical removal of the primary breast tumor, adjuvant treatment of women with tumors that are hormone receptor-positive decreases the odds of recurrence by more than 30%. Other antiestrogens that may have greater selectivity for breast estrogen receptors include raloxifene, toremifene, and fulvestrant.

Antiandrogens

Antiandrogens such as flutamide, bicalutamide, and nilutamide are competitive antagonists of the interactions between androstenedione and androgen receptors. Flutamide is a nonsteroidal antiandrogenic that possesses pure antiandrogenic activity when metabolized to its hydroxylated derivative. Administered with other drugs that decrease androgen production, flutamide is an effective treatment for hormone-dependent prostate cancer. Androgenic blockade results in feminizing side effects in men, including gynecomastia, hot flashes, and loss of facial hair. Skeletal muscle weakness and development of osteoporosis reflect a male menopause-like state. Flutamide can induce methemoglobinemia.⁴¹ Pulse oximetry readings in the presence of methemoglobinemia can overestimate the hemoglobin saturation levels. At levels of methemoglobinemia of greater than 35%, the pulse oximetry readings tend to approach a minimal level of 85%.⁴²

Aromatase Inhibitors

Aromatase is an enzyme complex consisting of two proteins: aromatase cytochrome P450 (CYP19) and nicotinamide adenine dinucleotide phosphate cytochrome P450 reductase. Inhibition of aromatase blocks the conversion of androgens to estrone in peripheral tissues including breast tissue. The high affinity of the aromatase inhibitors anastrozole and letrozole for CYP19 results in intense inhibition of estrogen effects on responsive receptors. Inhibition of aromatase is an effective treatment for postmenopausal women with breast cancer, in which the greatest source of estrone comes from conversion of androstenedione to estrone in liver, skeletal muscles, and fat. Exemestane is a steroidal aromatase inhibitor that binds to the enzyme complex and promotes enzyme degradation.

A partial medical hypophysectomy is produced by luteinizing hormone-releasing hormone agonists, such as leuprolide, buserelin, and goserelin, which inhibit secretion of follicle-stimulating hormone and luteinizing hormone by downregulating receptors that respond to these hormones. The result is insignificant plasma concentrations of sex hormones and palliation of breast and prostate cancer.

Monoclonal Antibodies

Numerous antibody-based therapies for treatment of cancer have emerged and are commonly used. This class of drugs includes the monoclonal antibodies trastuzumab, pertuzumab, bevacizumab, alemtuzumab, rituximab, obinutuzumab, polatuzumab vedotin, daratumumab, etc., which target specific antigen sites on cancer cells.⁴³ The mechanisms of action of these agents are specific and varied depending on the target. Common side effects include infusion reactions and cytopenias.

Trastuzumab is a monoclonal antibody that binds to the human epidermal growth factor receptor 2 (HER2) protein. It mediates antibody-dependent cellular cytotoxicity by inhibiting proliferation of cells that overexpress the HER2 protein. Similarly, pertuzumab is a recombinant humanized monoclonal antibody that targets the extracellular HER2 dimerization domain. It thereby inhibits HER2 dimerization and blocks HER downstream signaling, which halts cell growth and initiates apoptosis. Because pertuzumab binds to a different HER2 epitope than trastuzumab, they are often used in combination to synergistically inhibit HER2 signaling more completely. Both are used to treat HER2+ breast cancers.⁴⁴ Bevacizumab is a recombinant, humanized monoclonal antibody which binds to and neutralizes vascular endothelial growth factor by which it prevents its association with endothelial receptors fms-like tyrosine kinase 1 and kinase insert domain receptor. This results in inhibition of angiogenesis and thereby halts microvascular growth and subsequently growth of all tissues including malignant tissue. Bevacizumab is currently used in the treatment of many solid tumors including cervical cancer, colorectal cancer, glioblastoma, hepatocellular cancer, non-small cell lung cancer, ovarian cancer, and renal cell cancer. Additionally, it is often discontinued several weeks prior to surgery because it can result in postoperative wound healing complications.

Alemtuzumab targets CD52, which is a nonmodulating antigen present on the surface of B and T lymphocytes, most monocytes, macrophages, natural killer cells, and a subpopulation of granulocytes. Antibody-dependent lysis of cells occurs after it binds to CD52. It is used to treat B-cell chronic lymphocytic leukemia. Common side effects include myelosuppression, rash, fever, and cytomegalovirus disease/viremia. More commonly, rituximab is used to treat leukemias and lymphomas. Rituximab binds to a specific protein (CD20) that is expressed on the cell surface of B cells; the rituximab-CD20 complex appears to improve the effectiveness of natural killer cells in killing these diseased cells. Obinutuzumab is a glycoengineered type II

anti-CD20 monoclonal antibody used in the treatment of chronic lymphocytic leukemia and follicular lymphoma. It binds to the CD20 antigen expressed on the surface of pre-B- and mature B-lymphocytes, which activates complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, and antibody-dependent cellular phagocytosis that all result in cell death.⁴⁵ Polatuzumab vedotin is an antibody drug conjugate directed at CD79b, a B-cell specific cell surface protein commonly expressed in mature B-cell lymphomas.⁴⁶ This complex is internalized within the cell and produces monomethyl auristatin E, a microtubule-disrupting agent that induces cell cycle arrest in the G2/M phase and apoptosis. It is used to treat relapsed/refractory diffuse large B-cell lymphoma. Finally, daratumumab is a newer monoclonal antibody that binds to the CD38 glycoprotein found on hematopoietic cells and leads to cell death. It is commonly used in the treatment of multiple myeloma and amyloidosis. Common side effects of these drugs include infusion reactions and myelosuppression.

Other Targeted Therapies

Many targeted therapies continue to emerge and are employed in the treatment of various cancers. A few of the most notable are discussed in the following text. Imatinib is a tyrosine kinase inhibitor that binds to the extracellular domain of a specific tyrosine kinase (BCR-ABL) and inhibits this enzyme, which is responsible for cell proliferation in Philadelphia chromosome–positive chronic myelocytic leukemia. Major side effects include peripheral edema, liver function abnormalities, rash, and myelosuppression. Venetoclax is another targeted therapy that selectively inhibits the antiapoptotic protein BCL-2. BCL-2 is overexpressed in chronic lymphocytic leukemia cells and acute myeloid leukemia cells. Venetoclax binds to BCL-2 and restores the apoptotic process by displacing proapoptotic proteins. The major side effects of venetoclax are tumor lysis syndrome and neutropenia.

Sorafenib is a multikinase inhibitor that targets intracellular Raf kinases (CRAF, BRAF, and mutant BRAF) and cell surface kinase receptors (VEGFR1, VEGFR2, VEGFR3, platelet-derived growth factor receptor β [PDGFR- β], cKIT, FMS-like tyrosine kinase 3, rearranged during transfection [RET], and RET/PTC [papillary histotype]) to inhibit tumor growth and angiogenesis, whereas sunitinib does the same by inhibiting multiple receptor tyrosine kinases including platelet-derived growth factors (PDGFR α and PDGFR β), vascular endothelial growth factors (VEGFR1, VEGFR2, and VEGFR3), fms-like tyrosine kinase 3, colony-stimulating factor type 1 receptor, and glial cell line–derived neurotrophic factor (GDNF), which signals through activation of RET tyrosine kinase. Major side effects include diarrhea, hand-foot syndrome, stomatitis, and cardiotoxicity. Myocardial infarction is more of a concern with use of sunitinib.

Vaccines

Two types of vaccines aimed at preventing infection related to subsequent development of cancer have been approved by the U.S. Food and Drug Administration: vaccines against the hepatitis B virus, which can cause liver cancer, and vaccines against specific human papillomaviruses, which are responsible for the majority of cases of cervical cancer. Vaccines are also being developed that may include genetic manipulation of cancer cells to make them more antigenic and thus susceptible to immune responses. For example, virus-derived proteins expressed by virus-infected cancer cells can serve as promising sources of markers for vaccines to target. The U.S. Food and Drug Administration has approved one therapeutic cancer vaccine (sipuleucel-T) for certain men with metastatic castrate-resistant prostate cancer that is asymptomatic or minimally symptomatic. Sipuleucel-T is a cellular immunotherapy consisting of extracting autologous peripheral blood mononuclear cells (PBMCs) by leukapheresis (primarily dendritic cells that serve as antigen-presenting cells). The patient's PBMCs are then cultured (activated) with a recombinant human protein (PAP-GM-CSF) consisting of prostatic acid phosphatase linked to granulocyte-macrophage colony-stimulating factor. Prostatic acid phosphatase is a protein produced at abnormally high levels and overexpressed by prostate cancer cells. The patient's PBMCs are then reinjected into the patient every 2 weeks for a total of three times, stimulating T-cell immune response against prostate cancer cells. Side effects include severe infusion-related reaction, fevers, chills, fatigue, back pain, myalgias, and citrate toxicity.^{47,48}

Immunomodulatory Drugs

Immunomodulatory drugs are a novel class of orally available antineoplastic agents that are used to treat multiple myeloma. This class of drugs includes thalidomide, lenalidomide, and pomalidomide. Thalidomide is a first-generation immunomodulatory drug, whereas lenalidomide and pomalidomide are second-generation immunomodulatory drugs. They contain an imide group and work by producing antiproliferative, antiangiogenic, and immunomodulatory effects. Notable side effects of these drugs include somnolence, peripheral neuropathy, myelosuppression, venous thromboembolism, and teratogenicity.

Cancer Immunotherapies

Cancer immunotherapies is a class of cancer-directed therapy that has recently emerged over the past several years and includes immune checkpoint inhibitors and adoptive cell therapies. It has completely transformed the treatment algorithms for multiple solid tumor and hematologic malignancies due to the potential of these therapies to induce durable responses. Immune checkpoint inhibitors are usually used in the treatment of advanced disease and at times as adjuvant treatment. Immune checkpoint inhibitors bind to immune checkpoint proteins (cytotoxic T-lymphocyte-associated antigen 4 [CTLA-4] and programmed cell death-1 [PD-1]) as well as PD-1 ligands (PD-L1) expressed on multiple tissues including malignant tissues. Through this mechanism, they overcome tumor-mediated inhibition of T-cell function and reprogram T-cells to attack cancer cells and thereby induce antitumor responses. Disinhibition of T-cell function by immune checkpoint inhibitors can lead to a spectrum of inflammatory side effects affecting different organ systems collectively referred to as *immune-related adverse events* (i.e., pneumonitis, colitis, hypophysitis, hepatitis, nephritis, etc.). The exact pathophysiology driving this is not fully understood but is thought to be related to a combination of pathways involving autoreactive T cells, autoantibodies, and cytokines. The mainstay of therapy is typically corticosteroids and other immunosuppressive drugs in addition to temporarily holding or discontinuing further treatment with immune checkpoint inhibitors depending on severity. Duration of treatment may often last for several weeks depending on clinical course. Ipilimumab, nivolumab, pembrolizumab, atezolizumab, and durvalumab are the commonly used immune checkpoint inhibitors ([Table 42.4](#)).⁴⁹

TABLE 42.4

Immune checkpoint inhibitors and their approved indications in oncology practice in the United States^a

Class of agent and agent	Approved tumor types in the United States
CTLA-4 inhibitor	
Ipilimumab ^b	Melanoma ^c
PD-1 inhibitor	
Nivolumab ^b	Melanoma, ^c NSCLC, ^c RCC, ^c Hodgkin lymphoma, ^c UCC, ^c head and neck sqCC, ^c dMMR and MSI-H colorectal cancer, hepatoma
Pembrolizumab	Melanoma, ^c NSCLC, ^c Hodgkin lymphoma, ^c UCC, ^c head and neck sqCC, MSI-H or dMMR solid tumors, gastric and gastroesophageal junction cancers, cervical cancer
PD-L1 inhibitor	
Atezolizumab	UCC, ^c NSCLC ^c
Durvalumab	UCC, NSCLC (as consolidation after chemoradiotherapy for stage III)

Abbreviations: CTLA-4, cytotoxic T-lymphocyte antigen 4; dMMR, mismatch repair deficient; MSI-H, microsatellite instability high; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1; RCC, renal cell carcinoma; sqCC, squamous cell carcinoma; UCC, urothelial cancer.

^aData from Nishino M, Hatabu H, Hodi FS. Imaging of cancer immunotherapy: current approaches and future directions. *Radiology*. 2019;290(1):9-22.

^bIpilimumab and nivolumab combination therapy is also approved for metastatic melanoma and advanced RCC and for dMMR and MSI-H colorectal cancer.

^aThe indications have also been approved in the European Union.

Ipilimumab is a recombinant human immunoglobulin G1 monoclonal antibody that targets CTLA-4. Nivolumab is a fully human immunoglobulin G4 monoclonal antibody that selectively inhibits PD-1 activity by binding the PD-1 receptor and blocking PD-1 ligands (PD-L1 and PD-L2) from binding. Similarly, pembrolizumab is a highly selective anti-PD-1 humanized monoclonal antibody that works by using the same mechanism. In contrast, atezolizumab is a humanized monoclonal antibody immune checkpoint inhibitor that binds to PD-L1 to selectively prevent it from interacting with PD-1 and B7.1 (CD80) receptors. This restores antitumor T-cell function, which PD-L1 typically downregulates by binding to PD-1 and B7.1 (CD80) receptors. Similarly, durvalumab is a human immunoglobulin G1 \times monoclonal antibody, which works via the same mechanism. Whereas the combination of ipilimumab/nivolumab is used to treat metastatic melanoma, nivolumab and pembrolizumab are used alone and in conjunction with other cancer-directed therapies to treat a variety of solid tumors and Hodgkin lymphoma. Atezolizumab and durvalumab are typically used in the treatment of urothelial cancer and non–small cell lung cancer ([Tables 42.5](#) and [42.6](#)).

TABLE 42.5

Presentation of immune-related adverse events by organ system^a

Organ system	Presentation	
	Routinely reported events	Rare or infrequently reported events
Dermatologic	Rash (maculopapular, lichenoid), pruritus, vitiligo	Acneiform rash, alopecia, bullous pemphigoid, papulopustular rosacea, psoriasis, Stevens-Johnson syndrome, toxic epidermal necrosis, DRESS, Sweet syndrome
Gastrointestinal	Diarrhea, colitis, lichenoid mucositis	Enteritis, gastritis, pancreatitis
Endocrine	Hypothyroidism, hyperthyroidism, thyroiditis, hypophysitis	Autoimmune type 1 diabetes, primary adrenal insufficiency
Hepatic	Transaminitis, hepatitis	—
Respiratory	Pneumonitis	Pleuritis, sarcoidosis
Rheumatic	Arthralgia, inflammatory arthritis, myalgia	Dermatomyositis, myositis, polymyalgia-like syndrome, Sjögren syndrome, vasculitis
Renal	Increase in serum creatinine, nephritis	—
Ophthalmic	—	Uveitis, conjunctivitis, scleritis, episcleritis, blepharitis, retinitis
Neurologic	Sensorimotor neuropathy	Aseptic meningitis, autonomic neuropathy, encephalitis, facial nerve palsy, Guillain-Barré syndrome, myasthenia gravis, posterior reversible leukoencephalopathy, transverse myelitis
Hematologic	—	Aplastic anemia, hemolytic anemia, idiopathic thrombocytopenia purpura, lymphopenia, hemophilia
Cardiac	—	Cardiomyopathy, myocarditis, pericarditis

Abbreviation: DRESS, drug rash with eosinophilia and systemic symptoms.

^aReprinted with permission from Myers G. Immune-related adverse events of immune checkpoint inhibitors: a brief review. *Curr Oncol.* 2018;25(5):342-347. Copyright 2018 Multimed Inc.

TABLE 42.6

Management algorithm for immune-related adverse events by grade^a

Event type	Management considerations
Grade 1	<ul style="list-style-type: none"> Asymptomatic, minimally symptomatic, or radiographic or laboratory change Supportive care or localized therapy (or both) as outpatient Immune checkpoint inhibitor continued Increased monitoring
Grade 2	<ul style="list-style-type: none"> Mild-to-moderate or persistent symptoms Delay immune checkpoint inhibitor if corticosteroids are required.^b Oral corticosteroids (0.5-1 mg/kg)^c and supportive care as outpatient <i>Pneumocystis jiroveci</i> prophylaxis per institutional guideline and clinical judgment if 20 mg or more prednisone daily for more than 1 month; calcium and vitamin D; and prophylaxis for lower gastrointestinal bleed if risk factors are present Taper corticosteroids over at least 2-4 weeks when event reaches grade 1 or less. Increased monitoring; treat as grade 3 if symptoms persist.
Grade 3	<ul style="list-style-type: none"> Moderate-to-severe symptoms Delay immune checkpoint inhibitor; discontinue if risk exceeds benefit. Oral corticosteroids (1-2 mg/kg)^c as outpatient; consider intravenous route and hospitalization if symptoms persist for 48-72 hours, with or without additional immunosuppression^d if no response to intravenous corticosteroids in 48-72 hours. <i>Pneumocystis jiroveci</i> prophylaxis per institutional guideline and clinical judgment if 20 mg or more prednisone daily for more than 1 month; calcium and vitamin D; and prophylaxis for lower gastrointestinal bleed if risk factors are present. Taper corticosteroids over at least 4-6 weeks when event reaches grade 1 or less. Consider organ specialist consultation.
Grade 4	<ul style="list-style-type: none"> Life-threatening symptoms Hospitalization for intravenous corticosteroids (2-4 mg/kg),^c with or without additional immunosuppression^d if no response to intravenous corticosteroids in 48-72 hours. <i>Pneumocystis jiroveci</i> prophylaxis per institutional guideline and clinical judgment if 20 mg or more prednisone daily for more than 1 month; calcium and vitamin D; and prophylaxis for lower gastrointestinal bleed if risk factors are present. Taper corticosteroids over at least 4-8 weeks when event reaches grade 1 or less. Consult with organ specialist. Discontinue immune checkpoint inhibitor.

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^bImmune checkpoint inhibitor can be continued in grade 2 dermatologic or endocrine toxicity.

^cPrednisone equivalent.

^dAntithymocyte globulin, cyclophosphamide, infliximab, intravenous immunoglobulin, mycophenolate mofetil, tacrolimus, vedolizumab.

Adoptive Cellular Therapy

Chimeric Antigen Receptor T Cells

The chimeric antigen receptor (CAR) T cells are autologous T cells that have been genetically engineered to express the intracellular domain of a T-cell receptor fused to the antigen-binding domain of a B-cell receptor. These reprogrammed T cells recognize and attack tumor cells bearing the tumor-specific antigen when reinfused. The CAR T cells are currently used to target CD19, which is the pan B-cell antigen. Two CAR T-cell products are currently available. Tisagenlecleucel has been approved for treatment of refractory B-cell precursor acute lymphoblastic leukemia and diffuse large B-cell lymphoma, whereas axicabtagene ciloleucel has been approved for relapsed diffuse large B-cell lymphoma. Promising studies have shown the potential to

induce durable complete remissions in subsets of patients. Serious and potentially life-threatening side effects of these therapies include cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). CRS is thought to be due to T-cell activation after engagement of CAR T cells with their targets leading to systemic inflammatory response. This is often characterized by fevers, hypotension, respiratory failure, fatigue, and myalgias. It is generally treated based on grade. Broad-spectrum antibiotics and supportive care are used for low-grade CRS. Tocilizumab (interleukin 6 receptor antagonist) and high-dose steroids are used to manage severe CRS. ICANS, however, typically presents with a diverse range of neurologic symptoms including tremor, dysgraphia, mild expressive aphasia, apraxia, and impaired attention. Expressive aphasia is a specific symptom of ICANS. It is thought that ICANS may be due to diffusion of cytokines into the CNS or trafficking of CAR T cells into the CNS. Treatment usually involves high-dose steroids, and tocilizumab is not particularly effective in treating ICANS but may be administered to treat concurrent severe CRS.⁴⁹

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Psychopharmacologic Drugs*

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Psychopharmacologic therapeutics comprise a range of medicines targeting diverse aspects of central nervous system neuronal function. They include drugs developed primarily for psychiatric indications as well as those “borrowed” from neurology, anesthesiology, and other fields of medicine. Although traditionally organized by indication (eg, anxiolytics, antidepressants, antipsychotics) or by chemistry (eg, benzodiazepines, tricyclics, phenothiazines), the increasing application of particular medication classes across diagnostic boundaries—and growth in the number and diversity of compounds—has made such classification systems untenable. A recent initiative has thus sought to rationalize and destigmatize nomenclature via reference to the pharmacologic target and presumed mode of action of each drug.^{1,2} This chapter attempts to incorporate this emerging organizational framework into the traditional categories by indication.

The development of relatively safe and effective psychotherapeutic drugs now permits the vast majority of individuals with psychiatric disorders to be treated in ambulatory settings. Medications for adults with depressive mood disorders or anxiety are most typically prescribed by primary care physicians, although those with severe or persistent mental illness are more often treated by psychiatrists. Psychotropic medication use is prevalent and growing: The National Center for Health Statistics reported in 2017 that 12.7% of Americans older than age 12 years had used antidepressant medications in the past month, with markedly higher rates in women, non-Hispanic white Americans, and the elderly.³ Data for antipsychotic medications similarly confirms widespread use, with nearly 24 million prescriptions issued in the United States in 2017 for just the top 6 most commonly prescribed antipsychotic drugs.⁴

It is widely accepted that anesthesia can be safely administered to patients who are using medications for treatment of mental illness.^{5,6} There appears to be growing acceptance that the problem of drug interactions between psychopharmacologic drugs and drugs administered in the perioperative period is less than previously perceived and that past recommendations for discontinuation of antidepressant therapy are not justified. Nevertheless, vigilance for potential drug interactions remains important.⁷ In particular, many psychotropic and anesthetic drugs interact with various receptors for serotonin and are metabolized by common liver enzymes. This is particularly important in elderly patients, who use psychotropic medications at higher rates and who are at particular risk for toxicity. Furthermore, the anesthesiologist needs to understand the pharmacology as well as the expected and potential side effects of the drugs on which their patient is maintained. This chapter provides these important details.

Drugs With Primarily Serotonergic Activity

The majority of drugs classified by indication as “antidepressants” have impacts on either serotonergic neurotransmission or on both serotonergic and noradrenergic neurotransmission.⁸ Considering the wide range of disorders for which these drugs are effective—including diverse manifestations of depressive, anxiety, and chronic pain disorders—the term *antidepressant* has become a misnomer (**Table 43.1**). The broad spectrum of effectiveness of the antidepressant drugs does not imply a common pathophysiology but rather reflects the diverse roles of monoamine neurotransmitters in the human nervous system.

TABLE 43.1

Clinical uses of drugs with primarily serotonergic activity

Major depressive disorder

Depressive episodes of bipolar disorder

Panic disorder
Social phobia
Posttraumatic stress disorder
Obsessive-compulsive disorder
Bulimia nervosa
Neuropathic pain
Migraine prophylaxis

Mechanisms of Action

The precise mechanisms by which the serotonergic drugs work is unknown, but their direct actions serve to increase the amount of serotonin in synapses or to alter serotonin receptor signaling. Nevertheless, the characteristic time course of clinical improvement with these drugs is not explained by these acute effects. Neurobiologically, increases in synaptic serotonin or action at serotonin receptors occur promptly after initiation of antidepressant therapy; yet, clinical improvement typically does not occur for 2 to 4 weeks. Symptomatic improvement has thus been suggested to reflect a number of adaptive changes resulting from chronic exposure to these drugs. Such changes may include the desensitization of serotonin 5-HT_{1A} inhibitory autoreceptors, which at baseline respond to extracellular serotonin by downregulating presynaptic serotonin release and thus constrain serotonin levels, changes in synaptic plasticity of mood and anxiety-relevant neural circuits via drug-mediated effects on neurotrophic signaling pathways, or changes in hippocampal neurogenesis.⁹⁻¹²

Serotonin Receptors

Serotonin signaling is mediated by a large family of serotonin receptors, organized into seven families: six of which signal via excitatory or inhibitory G proteins and one of which (5-HT₃) is a ligand-gated cation channel. Receptors are found throughout tissues of the body, and serotonin signaling regulates a diverse array of processes outside of the central nervous system (CNS), including gastrointestinal motility, genital arousal, vascular tone, hematopoiesis, platelet aggregation, and aspects of the inflammatory response.¹³ In the CNS, serotonergic projections emanate broadly from a small group of neurons in the raphe nuclei of the brainstem—reaching targets throughout the cortex, subcortex, cerebellum, and spinal cord and regulating the release of a broad array of neurotransmitters and peptide hormones. Serotonin thus influences a broad array of social, affective, and cognitive functions including mood, sleep, aggression, appetite, sex, and memory.¹⁴ Although the specific relation of various receptor subtypes to behaviorally relevant circuits and clinical outcomes is poorly understood and beyond the scope of this chapter, a few specific receptors warrant particular mention. As noted earlier, the inhibitory receptor 5-HT_{1A} is of particular relevance to antidepressant responses—both as an autoreceptor regulating serotonergic neuronal activity and also postsynaptically in target tissues relevant to the neurogenic effects of antidepressant treatment.^{9,12} The excitatory 5-HT_{2A} receptor—agonized by the second-generation “atypical” antipsychotic (SGA) drugs and agonized by hallucinogens such as lysergic acid diethylamide and psilocin—localizes to cortical layer 5 and serves to regulate aspects of cognition, attention, and working memory relevant to psychosis; 5-HT_{2A} signaling is further implicated in the most threatening manifestations of serotonin syndrome. Lastly, the 5-HT₃ receptor regulates nausea and vomiting and may be beneficially targeted by psychotropic medications with 5-HT₃ antagonist activity, such as mirtazapine, in addition to the dedicated 5-HT₃ antagonist antiemetic drugs.

Serotonin Reuptake Inhibitors

Considered broadly, the serotonin reuptake inhibitors (SRIs) comprise several classes of medications which bind and inhibit the serotonin transporter protein (SERT), blocking reuptake of serotonin from the synaptic cleft into the presynaptic neuron and thus enhancing serotonergic neurotransmission. They are among the

most widely used medications for treatment of psychiatric conditions. Specific classes of SRIs, the relevant drugs, and general indications are discussed in the following text.

Adverse Effects

Common side effects of SRIs include insomnia, agitation, headache, nausea, and diarrhea ([Table 43.2](#)). However, these side effects are typically transient—arising when SRIs are first introduced or when dosages are increased—and typically remit fully within a week or two of their emergence. One exception to this pattern, however, and a prominent cause of noncompliance with SRI therapy, is drug-induced sexual dysfunction. This typically dose-dependent adverse effect occurs in both men and women and typically manifests as a requirement for greater sexual stimulation in order to attain orgasm, or complete anorgasmia in more severe cases.¹⁵

TABLE 43.2

Comparative pharmacology of drugs with primarily serotonergic activity

	Sedative potency	Anticholinergic potency	Orthostatic hypotension
Selective serotonin reuptake inhibitors			
Fluoxetine	+	+	+
Sertraline	+	+	+
Paroxetine	+	+	+
Fluvoxamine	+	+	+
Citalopram ^a	+	+	+
Escitalopram	+	+	+
Serotonin-norepinephrine reuptake inhibitors			May cause hypertension in some individuals
Venlafaxine	+	+	+
Desvenlafaxine	+	+	+
Duloxetine	+	+	+
Milnacipran	++	++	+
Levomilnacipran	+	+	+
Tricyclic antidepressants^a			
Amitriptyline	+++	++++	+++
Amoxapine	+	+	++
Clomipramine	+++	+++	+++
Desipramine	+	+	++
Imipramine	++	++	+++
Nortriptyline	+	+	+
Serotonin multimodal drugs			
Vortioxetine	+	+	+
Vilazodone	+	+	+
Trazodone ^a	+++	+	+++
Nefazodone	+++	+	++
Serotonin agonist			
Buspirone	+	+	+
Norepinephrine and serotonin multimodal drugs			
Mirtazapine	+++	++	++
Doxepin	+++	++	++

Monoamine oxidase inhibitors

Phenelzine	+	+	+++
Tranylcypromine	+	+	+++
Isocarboxazid	+	+	+++
Selegiline	+	+	+++

Abbreviations: 0, none; +, mild; ++, moderate; +++, marked; +++, greatest.

^aMay produce cardiac dysrhythmias.

Treatment-Emergent Suicidality

In September 2004, the U.S. Food and Drug Administration (FDA) recommended a “black box” warning for newer antidepressant drugs—primarily selective serotonin reuptake inhibitors (SSRIs).¹⁶ This controversial warning was based on evidence that suicidal thoughts and behaviors—although not completed suicides—occurred in children and adolescents at higher rates during treatment with SRIs compared to placebo. This warning has been criticized as harmful, in as much as its issuance led to decreased rates of diagnosis and treatment for depressed children and adolescents, and no data has suggested any increase in suicidal behavior in adults taking SRI medications.¹⁷

Serotonin Reuptake Inhibitor Discontinuation Syndrome

Abrupt discontinuation of SRI medications can lead to withdrawal symptoms, and the SRI discontinuation syndrome has received increasing attention as a clinical concern influencing management.^{18,19} Withdrawal symptoms are most commonly associated with SRIs that have short elimination half-lives (eg, paroxetine, venlafaxine, duloxetine), and they rarely emerge during dose decreases but rather develop when medication is fully discontinued—typically 3 to 4 half-lives (2-3 days) after a last dose. Vulnerability to withdrawal effects is higher in patients with longer histories of SRI use. The SRI discontinuation syndrome may be associated with dizziness, flu-like myalgias, pronounced irritability, insomnia, and visual disturbances. Yet the most common and pathognomonic symptom is a type of paresthesia, commonly referred to as “brain zaps” and typically described as recurrent, momentary electrical shock-like sensations in the head. The SRI withdrawal symptoms do not respond to benzodiazepines but do remit rapidly with reintroduction of SRI medication.¹⁸ Although not considered medically dangerous, the constellation of withdrawal symptoms can be intensely distressing for patients and, in acute care settings, may complicate interpretations of clinical condition or response to therapies. As such, in the absence of explicit contraindications, outpatient SRI medications should be continued in acute care settings, particularly for those individuals with long histories of SRI use. When SRI medications must be discontinued, a gradual and “hyperbolic” tapering course is recommended, with large initial decrements followed by increasingly smaller steps as the taper progresses.²⁰

Bleeding Risk

Relevant to acute care and operative settings, SRI-associated bleeding risks have long been a focus of theoretical concern, given serotonin’s role in platelet aggregation. In older adults, SRI use has been associated with increased relative risk (although low absolute risk) of upper gastrointestinal bleeding and intracerebral brain hemorrhage.²¹⁻²³ At the same time, the combination of SRI medications with anticoagulant therapies is common and not specifically contraindicated, with a recent study finding no significant increase in major bleeding events for anticoagulated outpatients taking SSRIs.²⁰ In surgical settings, where understandably data aggregation is challenging given the diversity of surgical contexts in which SRI-related risks have been studied, a recent systematic review has suggested that risks of increased bleeding are real and should be weighed in context against the risks of medication discontinuation, including risks of symptom relapse or discontinuation syndrome.²⁴

Hyponatremia

Clinically significant hyponatremia is another potential complication of SRI medication relevant to acute care settings. Although decreases in serum sodium have been reported as an adverse effect of a number of different psychopharmacologic drugs, most attention has been given to the association between drugs used to treat depression and new-onset hyponatremia. A 2004 prospective longitudinal study of older adults with major depressive disorder who started the SRI paroxetine showed that 12% developed hyponatremia, defined as serum sodium below 135 mEq/L, with a mean time to onset of approximately 9 days after initiating the drug.²⁵ Urine osmolality and serum antidiuretic hormone analysis suggested that hyponatremia after paroxetine was consistent with the syndrome of inappropriate secretion of antidiuretic hormone. Subsequent population-based studies and reviews of case reports suggest that many classes of antidepressant medication can cause hyponatremia but that the risk with SRI medications is clearly higher than that seen with serotonin receptor modulating medications or the tricyclic antidepressant medications.^{26,27} The risk appears higher in women, the elderly, and those with cardiovascular comorbidity. Risk of hyponatremia appears to diminish with time after medication initiation. For chronic users of SRI medication, there appears to be no increased risk of new-onset hyponatremia. Thus, for acute care patients with clinically significant hyponatremia, use and duration of use of SRI antidepressants should be assessed. Recently initiated SRI antidepressants should be considered for discontinuation, and for those patients requiring antidepressant use, a switch to non-SRI medications, such as mirtazapine, may be considered.^{28,29}

Serotonin Syndrome

Serotonin syndrome, attributed to toxic levels of synaptic and extracellular serotonin, is a rare but serious complication of SRI use.^{30–32} It classically presents with the triad of neuromuscular excitability, autonomic nervous system excitability, and mental status changes (**Table 43.3**).^{33–35} Signs of neuromuscular excitability may include hyperreflexia, clonus, myoclonus, opsoclonus, or rigidity; autonomic changes may include diarrhea, tachycardia, hypertension, fever, diaphoresis, flushing, and mydriasis; mental status changes may range from insomnia, agitation, and anxiety through to confusion or coma. In severe cases, life-threatening hyperpyrexia and rigidity may lead to rhabdomyolysis, multiorgan failure, and disseminated intravascular coagulation.

TABLE 43.3

Serotonin syndrome and commonly mistaken diagnoses

Diagnosis	Inciting agent	Time course	Fever	Physical examination
Serotonin syndrome	Serotonergic agonists	<12 hours	>41°C	Mydriasis, drooling, sweating, hyperactive reflexes, agitation, coma
Anticholinergic syndrome	Muscarinic antagonists	<12 hours	<39°C	Mydriasis, dry mouth and skin, normal reflexes, delirium
Neuroleptic malignant syndrome	Dopamine antagonists	1-3 days after dosing	>41°C	Normal pupils, drooling, pallor, lead-pipe rigidity, hyporeflexia, alert mutism, coma
Malignant hyperthermia	Volatile anesthetic and/or succinylcholine	Onset immediate to 24 hours after administration	To 46°C	Normal pupils, mottled sweaty skin, total body rigidity, hyporeflexia, agitation

Adapted from Boyer EW, Shannon M. The serotonin syndrome. *N Engl J Med.* 2005;352(11):1112-1120.

Serotonin syndrome typically results from the combination of different classes of serotonergic medications—characteristically, and most dangerously, the combination of an SRI with a monoamine oxidase inhibitor (MAOI). It rarely results from the use of a single serotonergic medication at therapeutic doses, although a large case series described its occurrence in approximately 15% of SRI overdoses.³⁶ Rigidity and hyperpyrexia—the most severe consequences of serotonin syndrome—appear to reflect excessive stimulation via the 5-HT_{2A} receptor and thus causative agents are generally those drugs that broadly increase extracellular serotonin, including serotonin precursors, stimulants of serotonin release, SRIs, or MAOIs.³⁷

Serotonergic modulators that agonize specific serotonin receptors other than 5-HT_{2A} appear to present low risk. However, a number of nonpsychiatric or nonserotonergic medications may trigger serotonin syndrome in conjunction with SRI or other serotonergic medication use. These include linezolid; methylene blue; lithium; the opioids pethidine, tramadol, fentanyl, and dextromethorphan; stimulants such as amphetamine, methamphetamine, methylphenidate, and phentermine; muscle relaxants including cyclobenzaprine; and recreational drugs including ecstasy. Opioids deserve particular mention: Although many inhibit SERT and thus increase synaptic serotonin levels, additional mechanisms including disinhibition of serotonergic neurons³⁸ or direct engagement with serotonin receptors may underlie serotonin syndrome risk.³⁹ This risk of serotonin syndrome precipitated by opioid drugs was addressed in a 2016 FDA drug safety communication.⁴⁰ Drugs that cause rapid elevations in serum level of SRI medications via pharmacokinetic interactions may also lead to serotonin syndrome, including ciprofloxacin, fluconazole, ritonavir, and erythromycin.

Serotonin syndrome is of particular concern in the recovery room or intensive care unit (ICU) as serotonergic agonists—known or unknown—may have been administered during surgery, reflecting the many serotonergic agonists in common use during anesthesia. Symptoms of serotonin syndrome characteristically develop acutely, within hours after introduction of a causative medication. The rapidity of onset and its association with changes in pharmacotherapy serve to differentiate serotonin syndrome from other entities in differential diagnosis, such as alcohol withdrawal, encephalitis, and neuroleptic malignant syndrome (see [Table 43.3](#)). Prompt recognition is critical to limiting associated morbidity. Primary interventions include discontinuation of serotonergic medications and prompt initiation of supportive care, including benzodiazepines or other neuromuscular sedatives, intravenous (IV) fluids when indicated, and in life-threatening cases, cooling, paralysis, and ventilation. Animal studies and case report literature have suggested the benefit of 5-HT_{2A} antagonist interventions, including cyproheptadine. However, these interventions have not been systematically assessed in clinical trials.⁴¹

Selective Serotonin Reuptake Inhibitors

The paradigmatic class of SRI medication—the SSRIs—includes the drugs fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, and escitalopram. The SSRIs selectively block neuronal reuptake of serotonin and are among the most widely prescribed psychotropic medications. The SSRIs are first-line pharmacotherapy for the majority of depressive and anxiety disorders, including major depressive disorder, generalized anxiety disorder, panic disorder, social anxiety disorder, posttraumatic stress disorder, and obsessive-compulsive disorder.

Compared with the tricyclic medications (the historical antecedents of the SSRIs as first-line treatment for depressive and anxiety disorders), SSRIs have greatly reduced anticholinergic properties, minimally contribute to postural hypotension, do not cause delayed conduction of cardiac impulses, and do not appear to have a major effect on the seizure threshold. Perhaps the most important advantage of SSRIs compared with the tricyclic medications is their relative safety when taken in overdose.⁴²

Different SSRIs have different side effect profiles, and patients who do not respond to one drug or who fail to tolerate it may do well on a different SSRI.⁴³ Standard practice thus dictates trying more than one SSRI before moving to another class of medication. Although efficacy of the various SSRIs is generally similar, differences within this class of drugs are in anticholinergic effects, elimination half-lives, and propensity for pharmacokinetic interactions. Notably, **fluoxetine** is a potent inhibitor of CYP2D6 and a moderate inhibitor of CYP2B6 and CYP2C9, and it has a markedly longer elimination half-life than other SRI medications, at 3 to 6 days (half-life is prolonged with chronic use, as fluoxetine inhibits its own metabolism). In addition, fluoxetine has an active metabolite, norfluoxetine, with a half-life of up to 16 days, similarly longer with chronic administration. The long half-life of fluoxetine means that its discontinuation is rarely complicated by withdrawal syndromes but also means that a long period of washout (6 weeks) is required before MAOIs or other medications contraindicated with SRIs may be added. **Paroxetine** has a markedly shorter half-life, at 21 hours, and has more significant anticholinergic effects. Use of paroxetine is thus often complicated by anticholinergic adverse effects, and discontinuation is frequently complicated by withdrawal syndrome. **Sertraline** has a half-life of 25 hours and fewer cytochrome P450 (CYP450) enzyme interactions than

fluoxetine, although may be more likely to contribute to dyspepsia and other gastrointestinal symptoms. **Fluvoxamine**, FDA approved solely for obsessive-compulsive disorder, is relatively rarely used given its short half-life (12-22 hours) requiring twice-daily dosing, a higher incidence of gastrointestinal side effects with initiation, and potent inhibition of numerous CYP450 enzymes leading to many clinically significant drug-drug interaction risks. **Citalopram** and its active S-enantiomer **escitalopram** are both widely used and well tolerated, with minimal pharmacokinetic interactions. However, citalopram may cause dose-dependent QT interval prolongation, which can place patients at risk for torsades de pointes.^{44,45} Escitalopram may also prolong the QT interval but possibly to a lesser degree. Thus, citalopram should be used with caution in patients at risk for prolonged QT intervals.

Serotonin-Norepinephrine Reuptake Inhibitors

Many SRI medications have pharmacologic activities in addition to SERT blockade. The serotonin-norepinephrine reuptake inhibitors (SNRIs) inhibit the norepinephrine transporter (NET) as well as SERT and are commonly prescribed as first- or second-line medications for depressive and anxiety disorders. The SNRIs include **venlafaxine**, **desvenlafaxine**, and **duloxetine** as well as **milnacipran** and **levomilnacipran**. Although various analyses have suggested that more noradrenergic medications may have superior efficacy for treatment of depression, any greater benefit of SNRIs is weighed against suggestions of poorer tolerability and concerns related to the potential hemodynamic consequences of increased noradrenergic tone.^{46,47} Although statistically significant elevation of systolic and diastolic blood pressure is observed with SNRI versus SSRI medications, observed blood pressure elevations are generally not clinically significant.⁴⁸ Other suggestions of increased risk relative to benefit for SNRIs include, for venlafaxine at least, elevated overdose-associated risk associated with proconvulsant and cardiac side effects.⁴⁹

Utility in Chronic Pain Syndromes

One symptom domain for which SNRI medications do clearly have superior efficacy over SSRI medications is for chronic pain.^{50,51} Together with the norepinephrine reuptake inhibitor tricyclic medications, SNRIs are commonly used off-label to treat various forms of chronic pain. Duloxetine and milnacipran have FDA-approved indications for the treatment of specific chronic pain syndromes. Although comparative efficacy for chronic pain of SNRIs versus tricyclics or other noradrenergic medications is not established—in part as the variability of pain syndromes studied limits comparison—these medicines are thought to work by increasing engagement of descending pain systems that suppress ascending pain transmission and regulate pain homeostatically.⁵² The emergence of benefit for pain at doses lower than those used for depression—and the more rapid onset of analgesic benefit than antidepressant benefit—suggests that mechanisms of treatment for these two distinct conditions are different.⁵⁰

Tricyclic Serotonin Reuptake Inhibitors

The broad category of SRI medications also includes **clomipramine**, a tricyclic medication with FDA approval for the treatment of obsessive-compulsive disorder, and **imipramine**, a tricyclic medication approved for treatment of depression and childhood enuresis. Clomipramine is a potent inhibitor of SERT, while imipramine potently inhibits both SERT and NET. The major metabolites of both medications, desmethylclomipramine (DCMI) and desipramine, respectively, additionally function as NET inhibitors, and thus, both medicines functionally serve as SNRIs. Like other tricyclic medications, clomipramine and imipramine have significant anticholinergic and antihistaminergic properties as well as greater propensity for related adverse effects, including cardiac dysrhythmia; so drug levels should be obtained as a routine aspect of patient management when doses are increased, new pharmacokinetic interactions are encountered, or toxicity is suspected.

Notably, the major metabolite of clomipramine, DCMI, like other tricyclic compounds, is predominantly noradrenergic. Attention should be paid to clomipramine versus DCMI plasma levels when drugs with inhibition of cytochromes 2D6 or 3A4 are added; yet, 3A4 inhibition via grapefruit juice has also been suggested as a therapeutic adjunct to alter clomipramine to DCMI ratios and increase the relative serotonergic activity of orally administered clomipramine.⁵³

Serotonin Multimodal Drugs

A number of drugs modulate specific serotonin receptors in addition to SERT blockade. These “multimodal” serotonergic drugs include **vortioxetine** and **vilazodone**, both of which are partial agonists at the 5-HT_{1A} receptors in addition to their primary SRI activity. Vortioxetine additionally acts as an antagonist at other serotonin receptors 5-HT₃ and 5-HT₇. The efficacy in major depression and the adverse effect profile of these medications is generally similar to that of the SSRIs, although vortioxetine may have additional benefit for depression-related cognitive impairment.⁵⁴ Vortioxetine notably has a long half-life, at 66 hours, whereas the half-life of vilazodone is approximately 25 hours, similar to that of the nonfluoxetine SSRIs.

Trazodone is another multimodal serotonergic drug, formally indicated for treatment of major depressive disorder but far more widely used at low dose as a safe and nondependency forming hypnotic for insomnia. Although it has some SRI activity, it is distinct from vilazodone and vortioxetine, particularly at low doses, in that its effects are primarily through serotonin receptor modulation, particularly antagonism of 5-HT_{2A} receptors and weaker 5-HT_{1A} partial agonism. Its efficacy as a hypnotic may reflect its 5-HT_{2A} antagonism as well as weak histamine H₁ receptor agonism and potent α₁ antagonism. Anticholinergic activity is minimal. An α₁ antagonism contributes to orthostasis and dry mouth as prominent side effects of the medication as well as the risk of priapism. Trazodone lacks effects on conduction of cardiac impulses but, on rare occasions, has been associated with cardiac dysrhythmias. The half-life of trazodone is relatively brief (3-9 hours). Notably, an active metabolite of the medication, meta-chlorophenylpiperazine, may contribute to false positives on urine tests for 3,4-methylenedioxymethamphetamine (MDMA). Toxicity associated with an overdose is less than what accompanies overdose of tricyclic drugs or MAOIs. Although relatively contraindicated in combination with MAOIs due to risk of serotonin syndrome, given minimal SRI activity at low doses, low-dose trazodone has been used in combination with MAOIs for treatment of MAOI-emergent insomnia in a case series and an open-label study.^{55,56}

Nefazodone is chemically related to trazodone, but with fewer α₁-adrenergic blocking properties. Like trazodone, nefazodone works primarily via 5-HT_{2A} antagonism and 5-HT_{1A} agonism, and it similarly weakly inhibits reuptake of serotonin. Unlike trazodone, nefazodone also weakly inhibits norepinephrine and dopamine reuptake. Despite significant α₁ antagonism, the risk of priapism may be less than that conveyed by trazodone. It has antihistaminergic activity, and thus is significantly sedative, but has minimal anticholinergic activity. The principal side effects are nausea, dry mouth, and sedation. Orthostatic hypotension may occur. Nefazodone-induced inhibition of CYP450 results in elevated plasma concentrations of benzodiazepines, antihistamines, and of protease inhibitors used in the treatment of human immunodeficiency virus infection. Rare cases of serious hepatotoxicity have been reported in association with nefazodone use, and liver enzymes should be monitored after initiation. Combination therapy with an MAOI is not recommended.

Serotonin Agonist

Buspirone is a serotonin agonist indicated for the short-term treatment of generalized anxiety disorder. This drug is a partial agonist at serotonin receptors, particularly 5-HT_{1A}, resulting in decreased serotonin turnover and anxiolytic effects. Downstream effects include elevations in cortical norepinephrine and dopamine, which may be attributable to the α₂-antagonist activity of a major metabolite, 1-(2-pyrimidinyl)piperazine.⁵⁷ As an anxiolytic, buspirone has no direct effects on γ-aminobutyric acid (GABA) receptors and thus no pharmacologic cross-reactivity with benzodiazepines, barbiturates, or alcohol. Buspirone lacks sedative, anticonvulsant, and skeletal muscle-relaxing effects characteristic of benzodiazepines. Absorption from the gastrointestinal tract is 100%, but extensive hepatic first-pass metabolism decreases bioavailability to 4%. The elimination half-time is 2 to 11 hours. Buspirone does not produce dependence and does not appear to be highly toxic if taken in overdose. The principal disadvantage seems to be a slow onset of effect (1-2 weeks), which may be interpreted as ineffectiveness by patients experiencing acute anxiety.

Serotonin and Norepinephrine Multimodal Drugs

Mirtazapine is a tetracyclic drug approved for treatment of major depressive disorder that functions—particularly at higher doses—to increase norepinephrine release through α_2 antagonism. It additionally is a 5-HT_{1A} agonist and antagonizes 5-HT_{2A} and 5-HT_{2C} receptors, activity that may facilitate antidepressant response by increasing cortical norepinephrine and dopamine release.⁵⁸ It is additionally a potent H₁-blocking antihistamine. Mirtazapine's antihistamine activity makes it highly sedating, and together with its 5-HT_{2C} antagonism, highly appetite stimulating. The sedation and weight gain limit its clinical use but make it a helpful drug for those suffering with depression characterized by insomnia and anorexia. Its 5-HT₃ antagonism further renders it an effective antiemetic. It is thus often used for medically ill, depressed patients, for example, those experiencing nausea and anorexia in conjunction with cancer treatment.⁵⁸ Mirtazapine has no appreciable SERT inhibition and no serotonin agonist activity. It thus does not cause sexual or other side effects typical of SRIs, nor is it thought to convey significant risk of serotonin syndrome. Furthermore, it has little anticholinergic activity and relatively low cardiac toxicity in overdose.

Doxepin is a tricyclic norepinephrine and serotonin multimodal drug, approved for treatment of depression and insomnia (at low dose), and yet differs from mirtazapine in that it is a potent SERT and NET inhibitor. It functions as a 5-HT_{1A} agonist and as an antagonist at multiple receptors, including α_1 , 5-HT_{2A}, 5-HT_{2C}, and muscarinic acetylcholine receptors. It is also a highly potent H₁ antihistamine, which contributes to its benefit at low dose as a hypnotic treatment for insomnia and as an antipruritic. **Amitriptyline** is similarly a tricyclic serotonin and norepinephrine multimodal drug, with both SERT and NET inhibition, indicated for major depressive disorder and at lower doses for chronic pain treatment. Amitriptyline additionally acts as an agonist or inverse agonist at 5-HT_{2A} and 5-HT_{2C} receptors as well as more weakly at 5-HT₃, 5-HT₆, and 5-HT₇ receptors. Like doxepin, it also has highly potent H₁ antagonism, resulting in significant sedative effects. The primary metabolite of amitriptyline is nortriptyline, itself an active NET inhibitor approved for treatment of major depressive disorder.

Like other tricyclics, doxepin and amitriptyline have significant anticholinergic side effects and are highly dangerous in overdose. Given potential for toxicity, monitoring of plasma level is essential at antidepressant doses and in the presence of relevant CYP450 inhibitors (2D6 for doxepin; 2C19 and 3A4 for amitriptyline). The mean elimination half-life of doxepin is 17 hours, with a more slowly cleared metabolite, nordoxepine, at 31 hours. Half-life for amitriptyline is variable, from 10 to 50 hours.

Monoamine Oxidase Inhibitors

Classed as serotonin, norepinephrine, and dopamine enzyme inhibitors (**phenelzine**, **isocarboxazid**, **moclobemide**, **selegiline**) or serotonin, norepinephrine, and dopamine multimodal drugs (**tranylcypromine**), the MAOIs constitute a heterogeneous group of drugs, which block the enzyme that metabolizes biogenic amines, increasing the availability of these neurotransmitters in the CNS and peripheral autonomic nervous system. Historically, MAOIs have been one of the most potent psychopharmacologic interventions for depressive disorders, but they are used much less commonly now because their administration is complicated by side effects (hypotension, insomnia), lethality in overdose, and lack of simplicity in dosing. In particular, most patients treated with MAOIs must follow specific diet guidelines because of the potential for pharmacodynamic interactions with dietary tyramine that can result in systemic hypertension ([Table 43.4](#)). However, many patients with major depression who do not respond to other antidepressants improve with MAOIs. Given their historical and ongoing importance in the psychopharmaceutical armamentarium, and unique risk of potentially dangerous drug-drug interactions, they are discussed in detail in the following text as a functional class.

TABLE 43.4

Dietary and drug restrictions in patients treated with monoamine oxidase inhibitors

Prohibited foods

Aged cheese

Cured, smoked, or processed meats

Preserved, salted, or pickled fish
Liver
Fermented soy products, including sauces
Yeast extracts
Fava or other broad beans
Dried or overripe fruits
Red wine, draft or homebrewed beer, some liqueurs
Prohibited drugs
Serotonin reuptake inhibitors (SSRIs, SNRIs, many TCAs)
Cold or allergy medications
Nasal decongestants
Sympathomimetic drugs
Opioids (especially meperidine)

Abbreviations: SNRIs, serotonin-norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

Monoamine Oxidase Enzyme System

Monoamine oxidase (MAO) is a flavin-containing enzyme found principally on outer mitochondrial membranes. The enzyme functions via oxidative deamination to inactivate several monoamines, including dopamine, serotonin (5-hydroxytryptamine), norepinephrine, and epinephrine. The MAO is divided into two subtypes (MAO-A and MAO-B) based on different substrate specificities ([Figure 43.1](#)).^{6,7} The MAO-A preferentially deaminates serotonin, norepinephrine, and epinephrine, whereas MAO-B preferentially deaminates phenylethylamine. Platelets contain exclusively MAO-A, and the placenta exclusively MAO-B. About 60% of human brain MAO activity is of the A subtype.

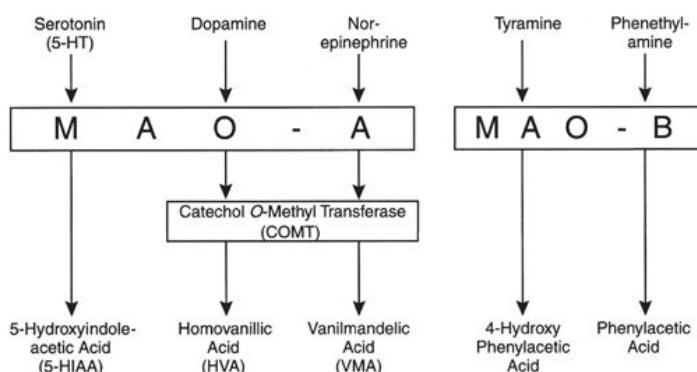


FIGURE 43.1 The two forms of monoamine oxidase enzyme (MAO-A and MAO-B) exhibit substrate selectivity. Reprinted with permission from Michaels I, Serrins M, Shier NQ, et al. Anesthesia for cardiac surgery in patients receiving monoamine oxidase inhibitors. *Anesth Analg*. 1984;63(11):1041-1044. Copyright © 1984 International Anesthesia Research Society.

Mechanisms of Action

The MAOIs act by forming a stable, irreversible complex with MAO enzyme, especially with cerebral neuronal MAO.⁵⁹ As a result, the amount of neurotransmitter (monoamines including serotonin, norepinephrine, and dopamine) available for release from CNS neurons increases. These effects, however, are not limited to the brain, and the concentration of monoamines also increases in the sympathetic nervous system. Because MAOIs cause irreversible enzyme inhibition, their effects are prolonged, as the synthesis of new enzyme is a slow process.

Due to its location in the outer mitochondrial membrane, MAO in neurons is only capable of deaminating substrates that are free within the cytoplasm and are unable to gain access to substrates once they are bound in the storage vesicles. As a result, cytoplasmic concentrations of monoamines are maintained at a low level.

Adverse Effects

The most common serious side effect of MAOIs is orthostatic hypotension, which may be especially prominent in elderly patients. Orthostatic hypotension may reflect accumulation of the false neurotransmitter octopamine in the cytoplasm of postganglionic sympathetic nerve endings. Release of this less potent vasoconstrictor in response to neural impulses is the most likely explanation for orthostatic hypotension as well as the antihypertensive effect that has been associated with chronic MAOI therapy.⁶⁰

Phenelzine has anticholinergic-like side effects and may produce sedation in some patients. Tranylcypromine has no anticholinergic side effects but has mild stimulant effects, which may cause insomnia and may contribute to transient increases in blood pressure commonly observed after dosing. Decreased libido and anorgasmia are serotonergic side effects of MAOIs. Some patients complain of paresthesias, which may respond to pyridoxine therapy. Weight gain is a common side effect of treatment with MAOIs, except for the stimulant-like tranylcypromine, which tends to be an appetite suppressant. Peripheral edema may also be seen with MAOI use. Hepatitis is a rare complication of MAOI therapy. Effects of MAOIs on the electroencephalogram (EEG) are minimal and not seizure-like, which contrasts with tricyclic antidepressants. Also in contrast with tricyclic antidepressants is the failure of MAOIs to produce cardiac dysrhythmias.⁶¹ Although elderly patients may be more susceptible to side effects, the dosage of MAOIs is the same in the elderly as in younger adults. Elderly persons often have higher levels of MAO, and the metabolism of these drugs does not seem to be affected by age.

Dietary Restrictions

The MAO enzyme present in the liver, gastrointestinal tract, kidneys, and lungs seems to perform a protective function in deactivating circulating monoamines. In particular, this enzyme appears to form the initial defense against monoamines absorbed from foods, such as tyramine and β-phenylethanolamine, which would otherwise produce an indirect sympathomimetic response and precipitous hypertension. The MAO-A is found in the gastrointestinal tract and liver, where it acts to metabolize bioactive amines such as tyramine. The MAOIs used in the United States as antidepressants inhibit MAO-A and MAO-B nonselectively. Selegiline, when used to treat Parkinson disease, selectively inhibits MAO-B, and patients do not need to follow a tyramine-free diet. At high doses (30 mg per day), however, even selegiline becomes a nonselective MAOI, making dietary precautions necessary (see [Table 43.4](#)). A form of selegiline has also been developed for transdermal administration in major depressive disorder, with aim to increase CNS levels while minimizing gut exposure. As with oral dosing, following a tyramine-restricted diet is not required with lower doses (6 mg/24 hours) but is required at higher doses (eg, 12 mg/24 hours).

Because patients treated with MAOIs cannot metabolize dietary tyramine and other monoamines, these compounds can enter the systemic circulation and be taken up by sympathetic nervous system nerve endings. This uptake can elicit massive release of endogenous catecholamines and result in a hyperadrenergic crisis characterized by hypertension, hyperpyrexia, and cerebral vascular accident. Therefore, patients taking MAOIs should be instructed to report promptly the onset of serious headache, nausea, vomiting, or chest pain. The precipitous hypertension resembles that which occurs with the release of catecholamines from a pheochromocytoma. In emergency settings, treatment of hypertension is with a peripheral vasodilator, such as nitroprusside. Cardiac dysrhythmias that persist after control of systemic blood pressure are treated with lidocaine or a β-adrenergic antagonist.

Drug Interactions

In addition to interacting with foods, MAOIs can interact adversely with opioids, ephedrine, tricyclic antidepressants, and SSRIs. These interactions can result in hypertensive crises or, most concerning, serotonin syndrome, characterized by CNS excitation, with potential for delirium, seizures, and death. Because MAOIs

are used uncommonly but have significant interactions with sympathomimetics and opioids that are commonly used in anesthesia, it is important for the anesthesiologist to be vigilant to identify them in the patient's medication list.

Opioids and Monoamine Oxidase Inhibitors

Administration of meperidine to a patient treated with MAOIs may result in an excitatory (type I) response (agitation, headache, skeletal muscle rigidity) or a depressive (type II) response characterized by hypotension, depression of ventilation, and coma.⁶² Enhanced serotonin activity in the brain (ie, serotonin syndrome) is presumed to be responsible for excitatory reactions evoked by meperidine. Meperidine is capable of inhibiting neuronal serotonin uptake. Slowed breakdown of meperidine due to *N*-demethylase inhibition by MAOIs is the presumed explanation for hypotension and depression of ventilation. About 20% of MAOI-treated patients experience excitatory reactions in response to meperidine. There is evidence that meperidine toxicity is increased only when both MAO-A and MAO-B are inhibited.⁷ Other opioids that are synthetic phenylpiperidines (fentanyl, sufentanil, alfentanil) have been associated with adverse reactions in patients treated with MAOIs, although the incidence seems to be less than with meperidine.⁶³ Morphine does not inhibit uptake of serotonin, but its opioid effects may be potentiated in the presence of MAOIs.⁶⁴ As noted previously, the FDA has warned about the risk of serotonin syndrome for all opioid medications when administered in conjunction with serotonergic drugs.⁴⁰

Sympathomimetics and Monoamine Oxidase Inhibitors

There is no experimental evidence to support the recommendation that all sympathomimetic drugs be avoided in patients treated with MAOIs. The most consistent observation has been an occasional patient who experienced an exaggerated systemic blood pressure response after the administration of an indirect-acting vasopressor such as ephedrine. The hypertensive response is presumed to reflect an exaggerated release of norepinephrine from neuronal nerve endings. If needed, the use of a direct-acting sympathomimetic (phenylephrine) is preferable to an indirect-acting drug, keeping in mind that receptor hypersensitivity may enhance the systemic blood pressure response to these drugs as well. Regardless of the drug selected, the recommendation is to decrease the dose to about one-third of normal, with additional titration of doses based on cardiovascular responses.⁷

Overdose

Overdose with an MAOI is reflected by signs of excessive sympathetic nervous system activity (tachycardia, hyperthermia, mydriasis), seizures, and coma. Treatment is supportive in addition to gastric lavage. Dantrolene has been suggested as a treatment for skeletal muscle rigidity and associated symptoms of hypermetabolism after an overdose with MAOIs.⁶⁵

Management of Anesthesia

In the past, it was a common recommendation to discontinue MAOIs 2 to 3 weeks before elective surgery based on the concern that life-threatening cardiovascular and CNS instability could occur during anesthesia and surgery when these drugs were present. This policy of drug withdrawal seems to be based more on anecdotes and isolated responses than on controlled scientific studies. Furthermore, discontinuation of effective therapy potentially places patients at risk for their psychiatric disturbances. There is general consensus that anesthesia can be safely administered in most patients being chronically treated with MAOIs.^{7,66-68} When anesthesia is administered to patients treated with MAOIs, it remains prudent to consider certain drug interactions and to avoid certain drugs, particularly meperidine.^{7,59}

Selection of Drugs Used During Anesthesia

The anesthetic technique selected should minimize the possibility of sympathetic nervous system stimulation or drug-induced hypotension. Regional anesthesia as in parturients is acceptable, recognizing that ephedrine should be avoided in the treatment of resulting hypotension.⁶² An advantage of regional anesthesia is

postoperative analgesia such that the need for opioids is negated or minimized. Etomidate and thiopental have been administered to MAOI-treated patients undergoing electroconvulsive therapy without adverse effects. Responses to nondepolarizing neuromuscular-blocking drugs are not altered by MAOIs.

Drugs With Primarily Noradrenergic Activity

Tricyclic and Related Antidepressants

In the decades prior to the approval and clinical implementation of the safer SSRI and SNRI drugs—in the late 1980s and early 1990s—**tricyclic antidepressant medications** were the standard of care for treatment of major depressive disorder. From a neuroscience-based nomenclature perspective, they are primarily norepinephrine reuptake inhibitors (particularly the secondary amines **desipramine** and **nortriptyline**). Yet, they also include drugs with both NET and SERT inhibition, or primary SERT inhibition (the tertiary amines **amitriptyline**, **imipramine**, **clomipramine**), as well as direct action at serotonin receptors, as noted previously. Despite their somewhat divergent functional activity; their shared side effect profile, pharmacology, and toxicities warrants consideration of these medications as a chemical class.

Mechanisms of Action

Tricyclic antidepressants act at several transporters and receptors, but their antidepressant effect is likely produced by blocking the reuptake (uptake) of serotonin and/or norepinephrine at presynaptic terminals, thereby increasing the availability of these neurotransmitters.

As with the more recently developed SRI medications, despite immediate effects of SERT and NET inhibition on increasing synaptic monoamine levels, therapeutic antidepressant effects typically only emerge after 2 to 3 weeks of treatment. It seems likely that potentiation of monoaminergic neurotransmission in the brain is only an early event in a complex cascade of events that eventually results in an antidepressant effect. Indeed, chronic administration of these drugs is associated with (1) decreased sensitivity of postsynaptic β_1 and serotonin 2 receptors and of presynaptic α_2 receptors and (2) increased sensitivity of postsynaptic α_1 receptors. Compared to other SRI drugs, tricyclics tend to be more sedative given their antihistaminergic potency, which may convey particular benefit for depressed patients with prominent insomnia.

Utility in Chronic Pain Syndromes

As with other SNRIs or norepinephrine reuptake inhibitors, tricyclic antidepressants may be useful in the treatment of chronic neuropathic pain and other chronic pain syndromes including fibromyalgia. Although there is no consensus on the mechanism of pain relief, beyond SERT and NET inhibition, potentiation of endogenous opioids in the CNS and antiinflammatory effects may contribute as mechanisms of benefit.⁶⁹ The antiinflammatory action of tricyclics has been shown in neuronal cell culture and may reflect structural similarities of tricyclic antidepressants to local anesthetics and known sodium channel blockade.^{58,70} In major depressive disorder, levels of an inflammatory marker, C-reactive protein, predict relative antidepressant benefit of nortriptyline over an SSRI.⁷¹ Because many chronic pain syndromes include an inflammatory component, it is possible that the clinical efficacy of tricyclic antidepressants in chronic pain patients is due to inhibition of an overactive inflammatory system.⁷² As with depression, the efficacy of tricyclic antidepressants for chronic pain syndromes may be limited by a narrow therapeutic index and tolerability of side effects.

Adverse Effects

Tricyclic antidepressants are highly effective, yet they have been supplanted as first-line drugs in many clinical situations because of their unfavorable side effect profile, largely resulting from their anticholinergic, antiadrenergic, and antihistaminic properties. The side effects of tricyclic antidepressants occur frequently and most commonly manifest as (1) anticholinergic effects, (2) cardiovascular effects, and (3) CNS effects (**Table 43.5**). Individual variation in the incidence and type of side effects may be related to the plasma concentrations of the tricyclic antidepressant and its active metabolites. Fortunately, the therapeutic window

for the treatment of chronic pain encompasses lower doses, and it is possible to measure plasma concentration to guide therapy.

TABLE 43.5

Pharmacologic treatment of tricyclic antidepressant overdose

Symptom	Treatment
Seizures	Diazepam Sodium bicarbonate Phenytoin
Ventricular cardiac dysrhythmias	Sodium bicarbonate Lidocaine Phenytoin
Heart block	Isoproterenol
Hypotension	Crystalloid or colloid solutions Sodium bicarbonate Sympathomimetics Inotropics

Data from Frommer DA, Kulig KW, Marx JA, Rumack B. Tricyclic antidepressant overdose: a review. *JAMA*. 1987;257(4):521-526, with permission.

Anticholinergic Effects

The anticholinergic effects of tricyclic antidepressants are prominent, especially at high doses. Amitriptyline causes the highest incidence of anticholinergic effects (dry mouth, blurred vision, tachycardia, urinary retention, slowed gastric emptying, ileus), whereas desipramine produces the fewest such effects (see [Table 43.5](#)). Anticholinergic delirium may occur in elderly patients even at therapeutic doses of these drugs. Serious anticholinergic toxicity may reflect the results of polypharmacy with more than one anticholinergic drug (eg, a tricyclic plus an over-the-counter preparation to treat diarrhea or insomnia). Elderly patients have greater sensitivity to anticholinergic effects.

Cardiovascular Effects

Orthostatic hypotension and modest increases in heart rate are the most common cardiovascular side effects of tricyclic antidepressants, presumably reflecting NET inhibition. Orthostatic hypotension may be particularly hazardous in elderly patients, who are at increased risk of fractures when they fall. The risk of hypotension during general anesthesia in patients treated with tricyclic antidepressants is low but has been reported.⁷³ Although cardiac dysrhythmia is a known risk of tricyclic overdose, at therapeutic levels, previous suggestions that tricyclic antidepressants increase the risks of cardiac dysrhythmias and sudden death have not been substantiated.⁷⁴ Furthermore, in the absence of severe preexisting cardiac dysfunction, tricyclic antidepressants at therapeutic levels lack adverse effects on left ventricular function and may even possess cardiac antidysrhythmic properties.⁷⁵ Orthostatic hypotension can be particularly problematic after ambulatory anesthesia and should be carefully anticipated on patients taking tricyclic antidepressants.

Tricyclic antidepressants depress conduction of cardiac impulses through the atria and ventricles, manifesting on the electrocardiogram (ECG) as prolongation of the P-R interval, widening of the QRS complex, and flattening or inversion of the T wave. Their quinidine-like properties may reflect slowing of sodium ion flux into cells, resulting in altered repolarization and conduction of cardiac impulses.

Nevertheless, changes on the ECG are probably benign and gradually disappear with continued therapy.⁷⁴

Central Nervous System Effects

Amitriptyline and doxepin produce the greatest degree of sedation. Weakness and fatigue are attributable to CNS effects and may resemble those seen in patients treated with phenothiazine dopamine antagonists. Tricyclic antidepressants—especially maprotiline and clomipramine—lower the seizure threshold, raising the

question of the advisability of administering these drugs to patients with seizure disorders or to those receiving other potentially proconvulsant drugs. Children seem to be especially vulnerable to the seizure-inducing effects of tricyclic antidepressants. Treatment with tricyclic antidepressants may enhance the CNS-stimulating effects of enflurane. Extrapyramidal reactions are rare, although a fine tremor develops in about 10% of patients, especially the elderly. The potential impact on neurologic diseases is important to consider when tricyclic antidepressants are prescribed for pain.

As mentioned earlier, tricyclic antidepressants have a narrow therapeutic index. Because of their cardiac toxicity, tendency to cause seizures, and depressant properties on the CNS, the tricyclic antidepressants may be fatal if taken in an overdose. Therapeutic plasma concentrations (parent drug plus the pharmacologically active demethylated metabolites) vary by drug but are typically in the range of 100 to 300 ng/mL, whereas toxicity is likely at levels greater than 500 ng/mL. Many individual tricyclic drugs have more clearly defined parameters: Plasma levels should not exceed 225 ng/mL when imipramine is administered; plasma levels should not exceed 125 ng/mL when desipramine is administered; the therapeutic range for nortriptyline is 50 to 150 ng/mL. When a patient treated with tricyclic antidepressants presents with signs and symptoms that could be due to mild toxicity, it is important to check a plasma concentration if possible prior to immediately stopping the drug or adding other commonly used serotonergic agonists and reuptake inhibitors. This important information will prevent sudden withdrawal or exacerbation in toxicity. This situation might occur in the ICU in a patient admitted for trauma when considering using a fentanyl infusion or in the chronic pain clinic in the common setting of polypharmacy.

Tolerance

Tolerance to anticholinergic effects (dry mouth, blurred vision, tachycardia) and orthostatic hypotension develops during chronic therapy with tricyclic antidepressants. Conversely, tolerance to desirable effects often fails to develop. As with SRI medications, it is preferable to taper tricyclic antidepressants when discontinuing. A mild withdrawal syndrome characterized by malaise, chills, coryza, and skeletal muscle aching may be attributable to super sensitivity of the cholinergic nervous system. These side effects may be difficult to differentiate from postoperative infection if these drugs are stopped acutely after surgery in the inpatient setting.

Pharmacokinetics

Tricyclic antidepressants are efficiently absorbed from the gastrointestinal tract after oral administration, reflecting high lipid solubility. Peak plasma concentrations occur within 2 to 8 hours after oral administration. Tricyclic antidepressants are strongly bound to plasma and tissue proteins, which, in combination with high lipid solubility, results in a large volume of distribution (up to 50 L/kg) for these drugs. The long elimination half-time (17-30 hours) and wide range of therapeutic plasma concentrations make once-daily dosing intervals effective.

Tricyclic antidepressants are oxidized by microsomal enzymes in the liver with subsequent conjugation with glucuronic acid. Metabolism varies 10- to 30-fold between individual patients and may be slowed in elderly patients, further supporting the critical role of plasma drug level monitoring. The elimination of tricyclic antidepressants occurs over several days, with 1 week or longer required for excretion. Many tricyclic compounds have active metabolites. Imipramine is metabolized to the active compound desipramine. Both these active compounds are inactivated by oxidation of hydroxy metabolites and by conjugation with glucuronic acid. Nortriptyline, which is the pharmacologically active demethylated metabolite of imipramine and amitriptyline, can accumulate to levels that exceed the precursors. Doxepin also appears to be converted to an active metabolite, nordoxepin, by demethylation.

Drug Interactions

The potential for toxicity related to excessive drug levels of the tricyclic medications, individual variation in metabolic rates, and need for drug-level monitoring, as noted in the preceding text, suggest that particular caution be applied with tricyclic drugs. Tricyclic antidepressants are principally metabolized by CYP450 1A2. Drugs commonly used for surgery and anesthesia that inhibit CYP450 1A2 including verapamil and

cimetidine would be likely to increase plasma concentrations. On the contrary, CYP1A2 inducers including rifampin, omeprazole, insulin, barbiturates, and carbamazepine reduce the peak concentrations and duration of action.⁷⁶ Fortunately, it is possible to measure the concentration of tricyclic antidepressants in the blood. This is particularly important in pain medicine where polypharmacy is the norm.

Sympathomimetics

The systemic blood pressure response to the administration of sympathomimetics to patients treated with tricyclic antidepressants is complex and unpredictable. It has been suggested that indirect-acting sympathomimetics may produce exaggerated pressor responses due to an increased amount of norepinephrine available to stimulate postsynaptic adrenergic receptors. Although acute administration of tricyclic antidepressants increases sympathetic nervous system synaptic activity due to norepinephrine reuptake blockade, chronic administration of these drugs may result in decreased sympathetic nervous system transmission due to downregulation of β -adrenergic receptors.^{77,78} It would appear that for patients recently started on tricyclic antidepressants, exaggerated pressor responses should be anticipated whether or not direct-acting or indirect-acting sympathomimetics are administered, although pressor responses may be more pronounced with an indirect-acting drug such as ephedrine. Smaller-than-usual doses of direct-acting sympathomimetics that are titrated to a specific hemodynamic response are recommended. For individuals chronically treated with tricyclic antidepressants (>6 weeks), administration of either a direct-acting or an indirect-acting sympathomimetic is acceptable, although a prudent approach may be to decrease the initial dose of drug to about one-third the usual dose. Conversely, conventional sympathomimetics may not be effective in restoring systemic blood pressure in patients chronically treated with tricyclic antidepressants because adrenergic receptors are either desensitized or catecholamine stores are depleted. In these patients, a potent direct-acting sympathomimetic such as norepinephrine may be the only effective management for hypotension.⁷⁹

Induction of anesthesia may be associated with an increased incidence of cardiac dysrhythmias in patients treated with tricyclic antidepressants. The tricyclic antidepressants are associated with arrhythmogenic activity, which may be a result from the potent blockade of cardiac sodium and potassium channels.⁸⁰

Anticholinergics

Because the anticholinergic side effects of drugs may be additive, the use of centrally active anticholinergic drugs for preoperative medication of patients treated with tricyclic antidepressants could increase the likelihood of postoperative delirium and confusion (central anticholinergic syndrome). Glycopyrrolate would theoretically be less likely to evoke this type of drug interaction in patients being treated with tricyclic antidepressants.

Antihypertensives

Rebound hypertension after abrupt discontinuation of clonidine may be accentuated and prolonged by concomitant tricyclic antidepressant therapy.⁸¹ Conceivably, increased plasma concentrations of catecholamines can persist for longer periods in the presence of tricyclic antidepressants that prevent uptake of norepinephrine back into sympathetic nerve endings.

Opioids

In animals, tricyclic antidepressants augment the analgesic and ventilatory depressant effects of opioids. If these responses also occur in patients, doses of these drugs should be carefully titrated to avoid exaggerated or prolonged depressant effects.

Monoamine Oxidase Inhibitors

The combination of a tricyclic antidepressant with SERT inhibition and an MAOI may result in potentially fatal serotonin syndrome. Although tricyclic medications are relatively contraindicated in combination with

MAOIs, this pairing of medications has been used historically by experts for patients with highly treatment-resistant illness.^{82–84}

Overdose

Tricyclic antidepressant overdose is life-threatening, as the progression from an alert state to unresponsiveness may be rapid.⁸⁵ Intractable myocardial depression or ventricular cardiac dysrhythmias are the most frequent terminal events. Presenting features of tricyclic antidepressant overdose include agitation and seizures followed by coma, depression of ventilation, hypotension, and hypothermia. Patients also present with striking evidence of anticholinergic effects including mydriasis, flushed dry skin, urinary retention, and tachycardia. The QRS complex on the ECG may be prolonged to greater than 100 milliseconds, and such prolongation beyond 100 milliseconds signifies increased likelihood of ventricular dysrhythmias and seizures.⁸⁶ The QRS prolongation in fact provides a better prediction of these events than plasma concentrations of tricyclic antidepressants, which have little predictive value.⁸⁶

The comatose phase of tricyclic antidepressant overdose lasts 24 to 72 hours. Even after this phase passes, the risk of life-threatening cardiac dysrhythmias persists for up to 10 days, necessitating continued monitoring of the ECG.

Treatment of a life-threatening overdose of a tricyclic antidepressant is directed toward management of CNS and cardiac toxicity (see **Table 43.5**).⁸⁵ Coma is frequently severe enough to require invasive airway support. Extrapyramidal effects and organic brain syndrome usually require supportive care only, although judicious use of physostigmine, 0.5 to 2 mg given IV, for treatment of anticholinergic psychosis may be indicated.

Seizures may precede cardiac arrest and should be treated aggressively with a benzodiazepine such as diazepam. After initial suppression of seizure activity, it may be necessary to provide sustained effects with a longer acting drug such as phenytoin. Acidosis associated with seizure activity may abruptly increase the unbound fraction of tricyclic antidepressant in the circulation and increase cardiac dysrhythmia risk. Alkalization of the plasma ($\text{pH} > 7.45$) either by IV administration of sodium bicarbonate or deliberate hyperventilation of the patient's lungs can temporarily reverse drug-induced cardiotoxicity. Lidocaine and phenytoin may be used subsequently to provide sustained suppression of cardiac ventricular dysrhythmias. Atropine is a useful treatment when tricyclic antidepressants dangerously slow atrioventricular or intraventricular conduction of cardiac impulses. Hypotension may be the result of direct tricyclic antidepressant-induced vasodilation, α -adrenergic blockade, or myocardial depression. Patients remaining hypotensive despite intravascular fluid replacement and alkalinization of the plasma may require systemic blood pressure support with sympathomimetics, inotropes, or both.

Gastric lavage may be useful in the early treatment, but this is most safely performed with a cuffed tracheal tube already in place. Activated charcoal significantly absorbs drugs throughout the gastrointestinal tract ("intestinal dialysis"). Conversely, avid protein binding of tricyclic antidepressants negates any therapeutic value of hemodialysis or drug-induced diuresis.

Other Norepinephrine Reuptake Inhibitor Drugs

The tetracyclic medication **maprotiline** is FDA approved for treatment of major depressive disorder and functions primarily like a secondary amine tricyclic with primary activity as an inhibitor of NET. It may, however, have additional effects as an antagonist at 5-HT_{2A} , 5-HT_7 , and α_1 receptors. Maprotiline is a potent antihistamine but differs from the tricyclic medications in that it is less anticholinergic. It is a CYP450 2D6 substrate and is highly protein bound with a mean elimination half-life of 51 hours. Toxicity and potential for interaction with anesthetic interventions (sympathomimetics, antihypertensives) is otherwise similar to that of the tricyclic medications.

Atomoxetine is a potent norepinephrine reuptake inhibitor with FDA approval for attention deficit hyperactivity disorder (ADHD) in children and adults. Although primarily an inhibitor of NET, animal and cell culture model experiments suggest it may also have activity on glutamatergic neurotransmission via *N*-methyl-D-aspartate (NMDA) antagonism.⁸⁷ As an NET inhibitor, it may potentiate the effect of

sympathomimetic drugs. Atomoxetine inhibits human ether-à-go-go-related gene (hERG) ion channel currents and may thus contribute to QT prolongation or predispose to arrhythmia in overdose.⁸⁸ Atomoxetine is a CYP450 2D6 substrate, and metabolism of atomoxetine is highly variable, with estimates of elimination half-life ranging from 4 to 19 hours. Measurement of atomoxetine concentration is not commonly available at clinical laboratories.

Norepinephrine Agonists

Familiar to most clinicians as antihypertensives, the α_2 agonist drugs **clonidine** and **guanfacine** have been usefully repurposed for the treatment of ADHD as non–dependency-forming alternatives or augmentations to the stimulant drugs. Both drugs have received FDA approval in long-acting formulations for treatment of ADHD in pediatric patients. Unlike the stimulants, which convey immediate attentional benefit, treatment effect of the α_2 antagonists may emerge more gradually with consistent use. Clonidine blocks a wide range of α_2 receptors, although guanfacine is highly selective for the α_{2A} receptor; thus, guanfacine may be less likely to cause the asthenic adverse effects of clonidine. Conversely, the broader antiadrenergic effects of clonidine have led to its off-label use for a number of indications, with varying levels of evidentiary support, including as a general anxiolytic, for the symptomatic management of opioid withdrawal, and for management of impulsivity and aggression in traumatic brain injury, borderline personality disorder, and other conditions. As with the cardiovascular use of these drugs, in addition to asthenia and dry mouth, rebound hypertension with abrupt discontinuation is a clinical concern, particularly when combined with β -adrenergic antagonist drugs.

Clonidine is also used in the neuraxis for pain management. A general barrier to use of drugs in the neuraxis is that proper neurotoxicology may not have been established during drug development and many of the drugs used are currently generic.^{89,90} Clonidine has a long history of use in intrathecal pumps for spasticity and analgesia. Its sole FDA indication for neuraxial use is in intrathecal pumps for intractable cancer pain. However, it is commonly used as an adjuvant in epidurals for childbirth and general surgery to facilitate local anesthetic sensory block.^{91,92} Its major dose-limiting side effect is hypotension and bradycardia. The antihypertensive effects of clonidine can be useful in the analgesic management of parturients with preeclampsia. It carries a black box warning for neuraxial use in labor and delivery that states “The risk of hemodynamic instability, especially hypotension and bradycardia, from epidural clonidine may be unacceptable in these patients. However, in a rare obstetrical, postpartum or perioperative patient, potential benefits may outweigh the possible risks.” Clonidine is also a commonly used adjuvant in peripheral nerve blocks, where it prolongs the action of local anesthetics.⁹³

Norepinephrine Dopamine Reuptake Inhibitor

Bupropion is one of the most widely prescribed psychotropic medications, with indications for treatment of major depressive disorder and for smoking cessation. It is also frequently used as a nonstimulant treatment for ADHD. Bupropion is structurally related to amphetamine—although is nondependency forming—and is thought to work via inhibition of dopamine and norepinephrine reuptake. As a first-line alternative to SSRI medications for treatment of depression, bupropion lacks the sexual side effects of serotonergic drugs. Bupropion is however associated with a greater incidence of seizures (about 0.4%) than other antidepressants, and some patients experience stimulant-like effects early in therapy that may exacerbate comorbid anxiety symptoms.⁹⁴ Bupropion has no anticholinergic effects, does not cause postural hypotension, and lacks significant effects on conduction of cardiac impulses. Bupropion is not associated with significant drug interactions. Ataxia and myoclonus have occurred rarely. Bupropion is relatively contraindicated with MAOIs given potential for hypertensive effects, and yet there is no theoretical basis for risk of serotonin syndrome. With a mechanism of action that includes inhibition of norepinephrine reuptake, it is not surprising that it has been evaluated for antineuropathic pain properties. There is some evidence for bupropion’s efficacy in neuropathic pain and inflammatory bowel disease.⁵⁰

Drugs With Primarily Dopaminergic Activity

Dopamine Norepinephrine Multimodal Drugs

Methylphenidate, like bupropion, blocks reuptake of both norepinephrine and dopamine via NET and dopamine transporter (DAT), respectively. Approved for the treatment of ADHD, methylphenidate is also a psychostimulant—increasing release of dopamine and, to a lesser extent, norepinephrine, through presynaptic mechanisms. Unlike related phenylethylamine-derived stimulants, methylphenidate appears to increase dopamine release through increasing presynaptic firing rates.⁹⁵ Common side effects of methylphenidate include appetite loss, nausea, insomnia, and anxiety. Methylphenidate may also exacerbate behavioral tics disorders. Use of the drug is associated with subjective palpitations and with mild increases in heart rate and blood pressure. Whether use of the drug may be associated with arrhythmia risk or cardiac morbidity/mortality risk is a subject of controversy and conflicting data.⁹⁶ Like other stimulant drugs, there is potential for tolerance and abuse, and with sudden discontinuation, withdrawal symptoms including fatigue, subjective cognitive cloudiness, and irritability may present. Overt risks of discontinuation are minimal, however, and holding stimulant medication in acute care settings is reasonable.

Mixed amphetamine salts (levoamphetamine and dextroamphetamine, marketed as Adderall) and **dextroamphetamine** are dopamine and norepinephrine multimodal drugs like methylphenidate that inhibit DAT and NET but also increase presynaptic dopamine release. Unlike methylphenidate, amphetamine blocks vesicular monoamine transporter 2, thus increasing presynaptic cytosolic dopamine and driving reverse transport through DAT. Amphetamines may have greater abuse liability and risk of tolerance/dependency than methylphenidate, and anesthesia providers should be aware of its abuse potential. An inactive prodrug of dextroamphetamine, **lisdexamfetamine**, requires hepatic metabolism for conversion into amphetamine and as such has a slower onset and longer duration of action, both felt to reduce abuse liability and dependency risk. Lisdexamfetamine is approved for both ADHD and binge eating disorder. Adverse effects of these stimulant drugs are similar to those of methylphenidate and include anxiety, insomnia, exacerbation of tics, and stereotypic behaviors as well as palpitations and mild increases in heart rate and blood pressure. The data is limited as to the effect these psychostimulants may have on the anesthetized patient when used at clinical doses, but it is commonly thought that the risk of intraoperative hemodynamic instability and arrhythmias may be increased. A small case study showed that patients who take chronic prescription amphetamines are hemodynamically stable during anesthesia.⁹⁷

Dopamine Reuptake Inhibitor Drugs

Modafinil and its purified enantiomer **armodafinil** are psychostimulant-like drugs that promote wakefulness. They are indicated for narcolepsy, shift-work sleep disorder, and obstructive sleep apnea. Classified as a dopamine reuptake inhibitor, modafinil is considered a highly selective and atypical DAT inhibitor.⁹⁸ Nonetheless, it has a complex pharmacodynamic profile and may further act through indirect promotion of histamine or orexin release.^{99,100} Tolerance and dependency risks are thought to be markedly less than those of amphetamines. Side effects of modafinil may include headache (common), nausea, and anxiety. Rare cases of Stevens-Johnson syndrome and other acute hypersensitivity reactions have been reported, leading to an FDA alert. As a CYP3A4 inducer, modafinil may reduce levels and thus efficacy of oral contraceptives and of opioid medications including fentanyl, oxycodone, and hydrocodone. Modafinil has been explored as an intervention to reduce postanesthesia recovery times in two small randomized studies. Although both studies showed subjective improvement in feelings of alertness and energy, the latter showed no benefit in psychomotor coordination.^{101,102}

Benztropine (also called benzatropine) is primarily anticholinergic, as a selective M₁ muscarinic acetylcholine receptor antagonist, yet also acts as an inhibitor of dopamine reuptake via DAT. However, it lacks the wakefulness promoting effects of modafinil or the reinforcing effects of methylphenidate or cocaine. It is most commonly used in conjunction with D₂ receptor-blocking drugs as a prophylactic for, or antidote to, acute drug-induced extrapyramidal symptoms (EPS). It is FDA approved for treatment of parkinsonism and for acute treatment of extrapyramidal side effects. Although indicated for acute treatment, it is not infrequently prescribed for chronic use, and as such, clinicians should be aware of the potential for additive anticholinergic effects, including urinary retention and delirium.

Dopamine Agonists

The nonergot dopamine D₃ receptor agonist drug **pramipexole** is approved for neurologic indications including Parkinson disease and restless legs syndrome. A number of smaller controlled trials and case report series have suggested the significant effect of pramipexole on depression in both bipolar II disorder and in treatment-resistant unipolar depression.^{103,104} The observation that pramipexole—but not L-dopa or other dopamine-increasing treatments—alleviates depressive symptoms in Parkinson disease has suggested that activity beyond D₃ agonism in the CNS may convey the drug's antidepressant benefit. In particular, pramipexole may have depression-relevant antiinflammatory action, perhaps via D₃ receptors on CD4 cells.¹⁰⁵ Side effects of pramipexole include common titration-rate-limiting nausea and the relatively rare but significant emergence of compulsive hedonic behaviors, including compulsive gambling, shopping, or sexual activity. Given the risks of dopamine agonist withdrawal syndrome, which has been reported for pramipexole use in Parkinson disease, a monitored taper off of pramipexole is recommended.¹⁰⁶ In perioperative context, case reports suggest the benefit of pramipexole for “restless limb” symptoms associated with general anesthesia.¹⁰⁷

Dopamine Antagonists

Dopamine antagonism, particularly at the D₂ receptor, has long been considered the central characteristic of medications used to treat psychosis.¹⁰⁸ The antipsychotic drugs are a chemically diverse group of compounds that are useful in the treatment of schizophrenia, severe bipolar disorder, depression with psychotic features, and certain organic psychoses (Table 43.6). These dopamine antagonist drugs are also used to treat Tourette disorder and certain movement disorders, and, given antiemetic effects of dopamine blockade, they are used for treatment of nausea and vomiting. Use for this latter indication became less common after a black box warning was placed on droperidol related to long QT syndrome. However, recently amisulpride—a D₂/D₃ antagonist that does not cause QT prolongation—has been found to be safe and effective for high-risk patients anesthetized with inhalational anesthetics.^{109–111}

TABLE 43.6

Comparative pharmacology of dopamine antagonist drugs

Category and drug	Sedative potency	Anticholinergic potency	Orthostatic hypotension potency	Extrapyramidal potency
Chlorpromazine	+++	++	+++	+
Thioridazine	+++	+++	+++	+
Fluphenazine	++	+	+	+++
Perphenazine	+	+	+	+++
Clozapine	+++	+++	+++	0
Loxapine	++	++	++	+++
Haloperidol	+	+	+	+++
Pimozide	+	+	+	+++
Risperidone	+	+	++	++
Olanzapine	+++	+++	++	+
Quetiapine	+++	++	++	+
Aripiprazole	+	+	+	++
Ziprasidone	++	+	++	+
Lurasidone	+	+	+	++
Amisulpride	+	+	+	++

Abbreviations: 0, none; +, mild; ++, moderate; +++, marked.

Historically, medications for psychosis have been divided into “first-generation” antipsychotic (FGA) and SGA drugs—the former functioning primarily as dopamine blockers, and the latter adding serotonin antagonism among other actions.

Mechanisms of Action

As a functional class, the efficacy of antipsychotic medications—as well as a number of risks and side effects—largely reflects their shared dopamine antagonist activity. Canonically, dopamine is believed to act via four primary projections in the brain: the mesolimbic, mesocortical, nigrostriatal, and tuberoinfundibular pathways.¹¹² Although the antipsychotic efficacy of these medications is believed to come primarily via their modulation of dopamine in the mesolimbic pathway, potent dopamine blockade via the mesocortical pathway may contribute to the negative cognitive and affective symptoms of schizophrenia, blockade of the nigrostriatal pathway underlies extrapyramidal side effects, and blockade of the tuberoinfundibular pathway contributes to endocrine effects of the medications. These risks are discussed in more detail in the following text. Antiemetic benefits of the dopamine antagonist drugs reflect action on dopamine receptors in the chemoreceptor trigger zone of the medulla. All antipsychotic drugs achieve maximum clinical efficacy over a period of weeks—emphasizing the importance of distinguishing the acute receptor antagonist effects of antipsychotic drugs from their chronic effects.

First-Generation Antipsychotics

The FGA drugs, including **chlorpromazine**, **thioridazine**, **perphenazine**, and **fluphenazine** (phenothiazine drugs), as well as **haloperidol**, **loxpipamine**, and **pimozide**, among others, are now infrequently used because the SGA drugs, which include serotonin 5-HT_{2A} antagonism, have been presumed to have greater benefit for the cognitive and affective aspects of psychotic disorders and lower risks of EPS, including tardive dyskinesia.¹¹³ Nonetheless, some FGA drugs remain commonly used in emergency or acute care settings (particularly haloperidol and chlorpromazine), and a landmark study failed to show greater efficacy for SGA drugs than an FGA comparator, perphenazine.¹¹⁴

Pharmacokinetics

The phenothiazine drugs have a high therapeutic index and relatively flat dose-response curve, accounting for the remarkable safety of these drugs over a wide dose range. Even large overdoses are unlikely to cause life-threatening depression of ventilation. These drugs do not produce physical dependence, although abrupt discontinuation may be accompanied by skeletal muscle discomfort. Phenothiazines often display erratic and unpredictable patterns of absorption after oral administration. These drugs are highly lipid soluble and accumulate in well-perfused tissues such as the brain. Passage across the placenta and accumulation of drug in the fetus is possible. Avid binding to protein in plasma and tissues limits the effectiveness of hemodialysis in removing these drugs.

Metabolism

Metabolism of phenothiazines is principally by oxidation in the liver followed by conjugation. Most oxidative metabolites are pharmacologically inactive. Metabolites appear primarily in urine and to a lesser extent in bile. Typical elimination half-lives of these drugs are 10 to 20 hours, permitting once-daily dosing intervals. The elimination half-time may be prolonged in the fetus and in the elderly, who have decreased capacity to metabolize these drugs.

Antiemetic Effects

The antiemetic effects of antipsychotic drugs reflect their interaction with dopaminergic receptors in the chemoreceptor trigger zone of the medulla. These drugs seem most effective in preventing opioid-induced nausea and vomiting. Perphenazine, 5 mg IV, has been shown to be as effective as ondansetron, 4 mg IV, for prevention of postoperative vomiting after gynecologic surgery.¹¹⁵ Unlike these other antiemetics, perphenazine was not associated with side effects such as sedation or hypotension, making this phenothiazine

derivative uncommon but potentially useful as an inexpensive prophylactic antiemetic. At 70 µg/kg IV, perphenazine decreases the incidence of vomiting in children during the first 24 hours after tonsillectomy.^{[116](#)}

Adverse Effects

The use of dopamine antagonist drugs may be complicated by serious side effects. Despite the common occurrence of side effects, however, these drugs have a large margin of safety and overdoses are rarely fatal. The serious side effects described in the following text are typically associated with the FGA medications, yet, with few exceptions, all are possible with the SGA drugs as well.

Extrapyramidal Effects

Acute dystonic reactions occur in approximately 2% of treated patients and are most likely to occur within the first 72 hours of therapy. Dystonic reactions are most common in young men and in patients taking high-potency D₂ antagonist drugs. Acute skeletal muscle rigidity and cramping may develop, usually in the musculature of the neck, tongue, face, and back. Opisthotonus and oculogyric crises may occur. The sudden onset of respiratory distress in a patient on neuroleptics may reflect laryngeal dyskinesia (laryngospasm).^{[117](#)} Acute dystonia responds dramatically to diphenhydramine (25-50 mg IV). Other forms of acute extrapyramidal side effects include drug-induced akathisia, characterized by restlessness, urges to move, and inability to tolerate inactivity, as well as drug-induced parkinsonism, characterized by tremor, masked facies, and skeletal muscle rigidity, especially in elderly patients. Patients with antipsychotic-induced akathisia often appear restless (inability to tolerate inactivity), which may be confused with the underlying psychotic disorder.

With chronic exposure to D₂ antagonist medications, late-appearing (tardive) extrapyramidal effects may emerge, including, most notoriously, tardive dyskinesia. Tardive dyskinesia may occur in 20% of patients who receive D₂ antagonist drugs for greater than 1 year, although it may occur even after only brief exposures to these drugs. Elderly patients and women of all ages seem to be more susceptible to the development of tardive dyskinesia. Manifestations of tardive dyskinesia include abnormal involuntary movements, which may affect the tongue, facial and neck muscles, upper and lower extremities, truncal musculature, and, occasionally, skeletal muscle groups involved in breathing and swallowing. Tardive dyskinesia may be exacerbated by withdrawal of the causative medication and only rarely remits. Compensatory increases in the function of dopamine activity in the basal ganglia may be responsible for the development of tardive dyskinesia. The FDA has recently approved two medication treatments for tardive dyskinesia—deutetrabenazine and valbenazine—both related to tetrabenazine and both of which inhibit the vesicular monoamine transporter 2 and thus decrease synaptic release of dopamine, serotonin, and norepinephrine.

Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome occurs in 0.2% to 1.0% of all patients treated with antipsychotic drugs.^{[118](#)} The emergence of the syndrome in the setting of dopamine antagonist drugs as well as the onset of the syndrome with abrupt withdrawal of levodopa therapy suggests a role of dopamine receptor blockade in the development of this syndrome. Risk factors for the development of neuroleptic malignant syndrome may include youth, male gender, dehydration, iron deficiency, catatonia, organic brain disease, and intercurrent illness.^{[119](#)} The syndrome typically develops over 24 to 72 hours and is characterized by (1) hyperthermia; (2) generalized hypertonicity of skeletal muscles; (3) instability of the autonomic nervous system manifesting as alterations in systemic blood pressure, tachycardia, and cardiac dysrhythmias; and (4) fluctuating levels of consciousness.^{[120](#)} Autonomic nervous system dysfunction may precede the onset of other symptoms. Increased skeletal muscle tone may so decrease chest wall expansion that it becomes necessary to provide mechanical support of ventilation. Skeletal muscle rigidity may be severe enough to cause myonecrosis leading to increased creatine phosphokinase levels, myoglobinuria, and renal failure. Liver transaminase enzymes are likely to be increased. Mortality may be greater than 5%, with common causes of death being ventilatory failure, cardiac failure and/or dysrhythmias, renal failure, and thromboembolism.^{[118](#)}

Treatment of neuroleptic malignant syndrome is primarily supportive, with emphasis on cessation of the dopamine antagonist treatments (or reinstatement of dopaminergic agonist medication when precipitated by withdrawal of dopamine agonists), ICU monitoring, IV hydration, cooling, and treatment of agitation and CNS arousal with IV benzodiazepines.^{118,119} The administration of the direct-acting muscle relaxant dantrolene and the dopamine agonists bromocriptine or amantadine with dopamine withdrawal is supported by case series and clinical literature but not by controlled trials.¹¹⁸ Electroconvulsive therapy is also applied clinically for treatment of neuroleptic malignant syndrome, although similarly without evidence from controlled trials.¹¹⁹

Malignant hyperthermia associated with anesthesia as well as the central anticholinergic syndrome may mimic the neuroleptic malignant syndrome.¹²⁰ A distinguishing feature is the ability of nondepolarizing muscle relaxants to produce flaccid paralysis in patients experiencing the neuroleptic malignant syndrome but not in those experiencing malignant hyperthermia (see [Table 43.3](#)).¹²¹

Cardiovascular Effects

Prolonged QTc Interval

Not restricted to the FGAs, yet long identified as a risk of their use, prolonged QTc syndrome warrants discussion as a general risk of psychotropic medication in the setting of anesthesia and a particular risk of the dopamine antagonists medications.¹²² Sudden death during treatment with haloperidol has been attributed to drug-induced prolongation of the QTc interval on the ECG.¹²³

Prolonged QTc syndrome is a malfunction of cardiac ion channels resulting in impaired ventricular repolarization that can lead to a characteristic polymorphic ventricular tachycardia known as torsades de pointes.¹²⁴ The single most common cause of the withdrawal or restriction of the use of drugs that are already in clinical use is the prolongation of the QTc interval on the ECG associated with torsades de pointes (polymorphic ventricular tachycardia).^{125,126} This prolongation most often results from delayed ventricular repolarization, a process that is mediated by the efflux of intracellular potassium. The channels responsible for the current are susceptible to blockade by many drugs, producing a suitable environment for the development of torsades de pointes, which may lead to sudden death. Nondrug factors associated with prolongation of the QTc interval include female gender, advanced age, electrolyte disturbances (hypokalemia, hypomagnesemia), congestive heart failure, bradycardia, myocardial ischemia, and congenital long QTc syndrome.

Several classes of noncardiac drugs commonly used in anesthesia (propofol, isoflurane, sevoflurane, succinylcholine, neostigmine, atropine, glycopyrrolate, metoclopramide, methadone macrolide and quinolone antibiotics, SSRIs, 5-HT₃ receptor antagonists, and dopamine antagonist drugs) produce dose-dependent prolongation of the QTc interval on the ECG in some patients.¹²⁵ Although these drugs can provoke torsades de pointes in susceptible patients, the risk of this response in patients with no other risk factors is minimal. Nevertheless, even in low-risk patients, drug interactions can lead to life-threatening torsades de pointes. These drug interactions are characterized by (1) additive or synergistic effects when two drugs capable of prolonging the QTc are administered (haloperidol and amitriptyline) or (2) the simultaneous administration of a drug that interferes with the metabolism of a second drug capable of prolonging the QTc interval (resulting increased plasma concentration of the second drug increases the risk of torsades de pointes). Drugs capable of inhibiting P450 enzyme and thus delaying the metabolism of second drugs capable of prolonging the QTc interval include calcium channel blockers, antifungal drugs, SSRIs, macrolide and quinolone antibiotics, antiretroviral drugs, and amiodarone. It is remarkable that long QT syndrome is not found in most general anesthesia, as propofol for induction, a volatile anesthetic for maintenance, and a 5-HT₃ antagonist for postoperative nausea and vomiting prophylaxis are such common companions. Fortunately, ECG monitoring is a standard during general anesthesia and in the recovery room, and we can be confident that if this were a common occurrence, we would be aware. We can only conclude that the personal predisposing factors cited earlier are an important factor in the occurrence of this potentially lethal arrhythmia.

When considering the effects of drugs on the QTc interval, it is important to recognize that it is difficult to measure this interval with precision.¹²⁷ There is inherent imprecision in identifying the end of the T wave

and variation in the onset of the QRS complex on some ECG leads providing different QTc values, depending on the leads selected for the measurement. Automatic QTc measurement techniques have been found to be less accurate in cardiac patients than in healthy controls. Indeed, calculation of the QTc interval is ambiguous, as there are numerous different formulas and each produces different results.

Drug administration route may also influence risk of dysrhythmia associated with QT prolongation. In 2007, the FDA formally warned against the administration of haloperidol IV—previously common practice for postoperative nausea and vomiting prophylaxis—given concerns for potentially higher risk of sudden cardiac death associated with QT prolongation. The IV administration of FGA drugs is thus discouraged. Intramuscular (IM) administration remains the standard for acute or emergency use of the FGA drugs.

Hypotension

Acute administration of chlorpromazine causes a decrease in systemic blood pressure resulting from (1) depression of vasomotor reflexes mediated by the hypothalamus or brainstem, (2) peripheral α -adrenergic blockade, (3) direct relaxant effects on vascular smooth muscle, and (4) direct cardiac depression. α -Adrenergic blockade produced by chlorpromazine is sufficient to blunt or prevent the pressor effects of epinephrine. Miosis that occurs predictably may also be due to α -adrenergic blockade. Some of the FGA drugs, including pimozide, also potently block calcium channels, which may contribute to their cardiac toxicity, including prolongation of the QTc interval on the ECG. Oral administration of the FGA drugs is associated with less pronounced systemic blood pressure-lowering effects. Indeed, tolerance to the hypotensive effect develops so that after several weeks of therapy, the blood pressure returns toward normal. Nevertheless, some element of orthostatic hypotension may persist for the duration of therapy.

Endocrine Effects

Dopamine antagonist medications increase prolactin levels disrupting the normal dopaminergic inhibition of prolactin secretion. Galactorrhea and gynecomastia may accompany excess prolactin secretion. Amenorrhea is a possible but rare complication of therapy. Decreased secretion of corticosteroids may be due to diminished corticotropin release from the anterior pituitary. Chlorpromazine may impair glucose tolerance and the release of insulin in some patients. Hypothalamic effects may manifest as weight gain and occasionally abnormalities of thermoregulation.

Sedation

Sedation produced by antipsychotic drugs appears to be due to antagonism of α_1 -adrenergic, muscarinic, and histamine (H_1) receptors. With chronic therapy, tolerance develops to the sedative effects produced by these drugs.

Obstructive Jaundice

Obstructive jaundice that is considered to be an allergic reaction occurs rarely 2 to 4 weeks after administration of phenothiazines. Indeed, there is prompt recurrence of jaundice if the offending drug, usually chlorpromazine, is again administered. If jaundice is not observed in the first month of therapy, it is unlikely to occur at a later date.

Hematologic Toxicity

Blood dyscrasias are rare but potentially life-threatening toxicities of the antipsychotic medications. Drug-induced agranulocytosis is most typically associated with the SGA drug clozapine but may occur in response to FGA drugs including chlorpromazine and haloperidol as well as other SGA drugs.¹²⁸ Routine monitoring of white blood cell is indicated, particularly during drug titration and in the early phase of treatment, and suspicion for agranulocytosis should accompany evaluation of fever in patients treated with antipsychotic medications.

Hypothermia

An effect of chlorpromazine on the hypothalamus is most likely responsible for the poikilothermic effect of this drug.

Seizure Threshold

Many antipsychotic drugs decrease the seizure threshold and produce a pattern on the EEG similar to that associated with seizure disorders. Chlorpromazine causes slowing of the EEG pattern, with some increase in burst activity and spiking. Sensory evoked potentials are often decreased in amplitude, and there is an increase in latency. It is unclear whether this can be problematic in their interpretation.

Skeletal Muscle Relaxation

Chlorpromazine causes skeletal muscle relaxation in some types of spastic conditions, presumably by actions on the CNS because the drug is devoid of actions at the neuromuscular junction.

Drug Interactions

The ventilatory depressant effects of opioids are likely to be exaggerated by antipsychotic drugs. Likewise, the miotic and sedative effects of opioids are increased, and the analgesic actions are likely to be potentiated. These drugs may interfere with the actions of exogenously administered dopamine, and the effects of alcohol are enhanced.

Dopamine and Serotonin Antagonist Drugs

The SGA drugs—also described as “atypical” antipsychotics—are thought to have decreased risk of extrapyramidal side effects relative to the FGA drugs. Although “atypicality” is poorly defined, these drugs include prominent antagonism at 5-HT_{2A} and other serotonin receptors in addition to their dopamine antagonist activity.¹²⁸ The SGA drugs come with similar overall risks and adverse effects as the FGA drugs, most notably potential extrapyramidal effects (including tardive dyskinesia and neuroleptic malignant syndrome), although relative risks may be reduced. More pronounced with the SGA drugs, however, are increased metabolic risks, including weight gain, hypercholesterolemia, and insulin resistance. Although pharmacologic mechanisms are unclear, direct impacts on these drugs on mechanisms of glucose homeostasis may convey risks for insulin resistance independent of weight gain.¹²⁹ These metabolic adverse effects conspire with more direct mediators of cardiac risk, including QTc prolongation, such that the SGA drugs are associated with higher rates of cardiovascular morbidity. Increased all-cause mortality in elderly patients using these drugs is a reason their use in management of dementia-related psychosis, in particular, is discouraged.

Despite these limitations, the SGA drugs have proven tolerable and effective in treating a broad range of psychopathology beyond primary psychotic disorders like schizophrenia. This is reflected by an increasingly broad range of FDA indications for individual drugs, including management of manic episodes, depressive episodes, and relapse prevention in bipolar disorder, augmentation treatment of major depressive disorder, management of irritability in autistic disorders, and treatment of Tourette disorder. They are also widely used off-label for treatment-resistant obsessive-compulsive disorder, severe personality disorders, and other conditions.

Clozapine

As an exception to the general model of D₂ antagonist-mediated antipsychotic efficacy, **clozapine** is the most effective of antipsychotic medications—often beneficial when other treatments fail—but has relatively little D₂ antagonist activity.¹³⁰ It also is the only antipsychotic medication that appears not to convey risk of tardive dyskinesia or extrapyramidal side effects.¹³¹ As the class-defining SGA, clozapine includes antagonist actions at 5-HT_{2A}, 5-HT_{2C}, 5-HT₆, and 5-HT₇ receptors. It additionally has potent antimuscarinic activity and α₁ antagonism. More recent literature has suggested that additional activities may contribute to therapeutic benefit, including GABA_B receptor agonism.¹³⁰

Despite its superior efficacy, clozapine is not a first-line medication, in part due to multiple potential medical complications of clozapine use, detailed in the following text. Despite these risks—perhaps because of its benefit for the underlying disorder—clozapine use in schizophrenia is associated with the lowest all-cause mortality of any antipsychotic drug.¹³² Clozapine is additionally the only medication for schizophrenia proven to decrease suicidality.¹³³

The most concerning adverse effect of clozapine is agranulocytosis. Although it occurs in less than 1% of patients; the patients, prescribers, and pharmacies must be registered with a central clozapine Risk Evaluation and Mitigation Strategy program.¹³⁴ In order to have access to the drug, patients must undergo mandatory weekly blood count monitoring for the first 6 months of treatment, and a reduced but ongoing schedule of monitoring thereafter.

Low-grade fever sometimes occurs early in the use of clozapine and sustained mild sinus tachycardia may be observed. More concerning potential cardiac effects include the development of potentially fatal clozapine-associated myocarditis, the basis for recommended testing of C-reactive protein and troponins weekly during clozapine initiation and titration.¹³⁵ Considered rare, this complication may be more likely in inpatient settings where clozapine is more rapidly titrated to therapeutic doses.¹³⁶ Inflammatory processes involving other organs, including hepatitis, nephritis, and pancreatitis, have also been attributed to clozapine.¹³⁷

Excessive salivation, especially during sleep, is a common but paradoxical and poorly explained effect of this strongly anticholinergic drug. Oral rinse with two drops of ophthalmic atropine solution in a glass of water is a potential treatment. Given the pronounced anticholinergic effects of clozapine, systemic anticholinergics should be avoided, and caution is advised when using clozapine in patients at risk for glaucoma, ileus, or urinary retention. These anticholinergic effects are also thought to contribute to clozapine's significant potential for constipation, which may be severe and even life-threatening if not managed assertively. Bowel function should be routinely monitored in individuals using clozapine.

Clozapine has been combined safely with lithium and antidepressant drugs, and the white blood cell count/augmenting effect of lithium may preserve clozapine treatment for patients with borderline low neutrophil counts.

Olanzapine

Olanzapine is structurally and pharmacologically similar to clozapine and similarly is one of the most effective antipsychotic medications, frequently used first line in acute care settings for agitated psychosis or bipolar mania, where it may be administered orally or via IM injection. Like clozapine, it is initially heavily sedating and associated with hypotensive effects; it also conveys among the strongest risks for weight gain and metabolic syndrome. Like other antipsychotic medications, olanzapine may disrupt thermoregulation and leave treated patients more susceptible to heat injury. Its efficacy and tolerability profile is otherwise superior, however.¹³⁰ Olanzapine's propensity for hypotension and its frequent acute care use intramuscularly, in situations where patients may also receive IM or IV benzodiazepines, has led to guidance from its manufacturer warning against coadministration of IM olanzapine and parenteral benzodiazepines due to risk of cardiorespiratory suppression and death.¹³⁸ The post-marketing data supporting this association have been challenged, however, and it has been suggested that this risk may be significant primarily in those patients already intoxicated upon presentation.¹³⁹ Olanzapine has an elimination half-time of 30 to 50 hours, with literature suggesting slower clearance in women and the elderly. It is metabolized by CYP450 enzymes 1A2 and 2D6.

Risperidone, Paliperidone, and Iloperidone

Risperidone is one of the most widely used SGA drugs and is available in long-acting injectable (LAI) form. It is considered one of the most effective and the most “first-generation”-like of the SGA drugs, given its potency as a D₂ antagonist, and may have greater risk of EPS compared with other SGA drugs. In addition to dopamine and serotonin antagonism, risperidone is a potent antagonist at α₁ and α_{2A} and α_{2C} receptors, which may account for the potential side effect of hypotension. Risperidone has been associated with

exaggerated systemic hypotension during a spinal anesthetic.¹⁴⁰ Related drugs include **paliperidone** and **iloperidone**. All have elimination half-lives on the order of 20 to 30 hours. Of the SGAs, risperidone and paliperidone are the most commonly associated with prolactin increase and gynecomastia. Iloperidone is less commonly associated with EPS or gynecomastia but may be overall less efficacious.¹³⁰ There is moderate evidence for the prophylactic use of risperidone to prevent delirium after cardiac surgery along with high-quality evidence confirming no increased risk of mortality.¹⁴¹

Aripiprazole, Brexpiprazole, and Cariprazine

Aripiprazole and related drugs **brexpiprazole** and **cariprazine** differ from other SGAs in that they are D₂ receptor partial agonist/antagonists, along with partial agonism or antagonist activity at multiple serotonin receptors including 5-HT_{1A}, 5-HT_{2A-C}, and 5-HT₇. Aripiprazole is one of the most widely used of the SGA drugs, in part given its balance of efficacy and tolerability. It is less likely to cause weight gain or sedation and is frequently used in mood disorders, in line with its FDA-approved indications for all phases of bipolar disorder as an adjunctive intervention in major depressive disorder. Particular side effects, in addition to general risks of the SGA drugs, include akathisia—typically associated with higher starting doses or too-rapid dose escalation—and the potential emergence of compulsive hedonic or risk behaviors, including compulsive gambling, shopping, or sexual behavior. This latter adverse effect may reflect aripiprazole's partial D₃ agonism and is similarly associated with D₃ agonist drugs pramipexole and ropinirole. Aripiprazole is less likely than most other SGA drugs to cause QT prolongation or hyperprolactinemia.¹³⁰ The elimination half-lives of aripiprazole, brexpiprazole, and cariprazine are relatively long, on the order of 3 to 5 days. All three drugs are substrates of CYP450 enzymes 2D6 and 3A4.

Ziprasidone and Lurasidone

Ziprasidone antagonizes D₂ and to a lesser extent D₃ receptors, antagonizes 5-HT_{2A} receptors, and is a partial antagonist at 5-HT_{1A} and 5-HT_{2C}. It is considered a moderately effective medication, prized primarily for its minimal metabolic impact compared to other SGA drugs. It notably is associated with QT prolongation to a greater extent than others, however, and its intestinal absorption depends strongly on food. **Lurasidone** is an antagonist at the dopamine D₂ and D₃ receptors as well as at the 5-HT_{2A}, 5-HT₇, and α_{2C} receptors. It also has partial agonist activity at the 5-HT_{1A} receptor and is minimally active at the 5-HT_{2C} receptor, potentially limiting its effects on appetite and weight. Although valued for its reduced metabolic risk, lurasidone is frequently accompanied by distressing akathisia, particularly when newly initiated or titrated too rapidly to higher dose ranges. Like ziprasidone, absorption is highly influenced by concomitant food intake. Lurasidone is primarily metabolized by CYP3A4, and its half-life is approximately 20 to 40 hours.

Amisulpride

An outlier among the atypical antipsychotics given minimal 5-HT_{2A} antagonism, **amisulpride** is nonetheless a potent D₂ and D₃ antagonist and an antagonist at 5-HT₇ receptors, the latter activity hypothesized to convey antidepressant effects. Although approved in Europe and many other regions outside the United States for treatment of psychotic disorders, in the United States, it has been approved only recently, at a markedly lower dose range and in IV formulation, for treatment of postoperative nausea and vomiting. Although the adverse effect profile of amisulpride at antipsychotic doses is similar to that of other atypical antipsychotic drugs with significant risk particularly of hyperprolactinemia and QTc prolongation,¹⁴² at the low-dose ranges used for postoperative nausea and vomiting, adverse effects are comparable to placebo,¹⁴³ and there are no clinically significant impacts on QTc.¹⁴⁴

Long-Acting Injectable Formulations

A number of drugs used for treatment of psychosis are available in LAI formulations, a dosing strategy aimed to limit nonadherence and symptomatic relapse. These include the dopamine antagonist drugs haloperidol and fluphenazine and the dopamine serotonin antagonist drugs olanzapine, aripiprazole, risperidone, and

paliperidone. Dosing schedules range from every 2 weeks (haloperidol) to every 3 months (paliperidone). Although use of LAI formulations typically follows a period of induction on oral medication, such that unexpected adverse effects should be limited, acute care providers should recognize that full drug washout may take months once injected, and as such, periods of susceptibility to adverse effects and drugs interactions may be similarly prolonged. Injection site irritation and rare complications of administration may also occur: LAI olanzapine is associated with rare occurrences of a postinjection delirium and sedation syndrome felt to represent local tissue injury and inadvertent distribution of olanzapine pamoate into blood, where it is rapidly dissolved into active drug. As with other depot formulations, in the anesthetic setting, it may not be obvious that the patient is being treated with a long-acting formulation. This is particularly problematic with opioid partial agonists but relevant for dopaminergic antagonists as well. The existence of these novel formulations and their potential use when unexpected side effects occur should be on every anesthesiologist's radar.

Dopamine Serotonin Norepinephrine Multimodal Drugs

Quetiapine, like other SGAs, has 5-HT_{2A} antagonism that is more potent than its D₂ receptor antagonism, which may be minimal at lower dose ranges. It notably has an active metabolite—norquetiapine—with potent NET inhibition and thus is considered a dopamine, serotonin, and norepinephrine multimodal drug. The EPS risk is the lowest of any antipsychotic drug with the exception of clozapine, and as such, it is often the antipsychotic of choice in situations when EPS risk is a concern, such as for psychosis associated with Parkinson disease.¹³⁰ It is significantly sedating at low doses—likely due to significant antihistamine activity—and may cause orthostatic hypotension given its α₁ antagonist activity. Antimuscarinic activity is minimal. Quetiapine levels are strongly influenced by CYP450 3A4 inducers (lamotrigine, carbamazepine) or inhibitors (ketoconazole). Elimination half-life is relatively brief, at 7 hours, and as such, an extended-release formulation of quetiapine has been marketed. Extended-release quetiapine has been found to have analgesic efficacy in a double-blind trial of patients with chronic comorbid depression and pain.¹⁴⁵

Drugs With Primarily Glutamatergic Activity

Glutamate Antagonists and Channel Blockers

Valproate, Carbamazepine, and Oxcarbazepine

The anticonvulsants **valproate** and **carbamazepine**, as well as the related drug **oxcarbazepine**, are used commonly in the treatment of bipolar disorder as antimanic and mood stabilizing interventions. The mechanisms of valproate are poorly understood, whereas carbamazepine and oxcarbazepine are thought to bind and inhibit inactive neuronal sodium channels, preventing repetitive action potential firing. As such, they are thought to impact primarily excitatory glutamatergic neurotransmission. Common side effects of valproate include sedation, double vision, tremor, alopecia, gastrointestinal disturbance, and potentially thrombocytopenia. Toxic encephalopathy related to hyperammonemia may also occur at higher doses or in overdose, which may benefit from carnitine supplementation.¹⁴⁶ Valproate is commonly used for migraine prophylaxis, where it has moderate efficacy.¹⁴⁷ Its use is complicated in a large portion of migraine sufferers—young women capable of childbearing—as it has been associated with an increased incidence of birth defects when taken during the first trimester. The pain practitioner should consider this factor when choosing one of the many potential drugs for headache prophylaxis in women with the potential for pregnancy.¹⁴⁸

Adverse effects associated with carbamazepine include hepatitis and hypersensitivity reactions such as Stevens-Johnson syndrome, with individuals carrying HLA-B*1502 felt to be at markedly higher risk. Carbamazepine is also associated with bone marrow suppression, including agranulocytosis and aplastic anemia. Carbamazepine is a CYP450 inducer and may decrease levels of medications, including valproate, warfarin, and oral contraceptives. It also accelerates the elimination of benzodiazepines.¹⁴⁹ Levels of carbamazepine may be increased by concomitant cimetidine, calcium channel blockers, or erythromycin. Oxcarbazepine is thought to be less vulnerable to metabolic interactions than carbamazepine and may have lesser risk of bone marrow suppression or anemia. Oxcarbazepine is commonly associated with decreased blood sodium, and severe hyponatremia may occur in up to 12% of those using the drug. Drug levels, liver

function tests, electrolytes, and complete blood counts should be followed in all patients being treated with these anticonvulsant drugs.

Lamotrigine

Lamotrigine is similarly a channel-blocking anticonvulsant drug that impacts glutamatergic signaling. It has an FDA indication for maintenance treatment in bipolar I disorder. It is generally better tolerated and less often associated with adverse reactions than valproate or carbamazepine; however, use in acute care settings is limited by the risk of Stevens-Johnson syndrome or other hypersensitivity reaction because this risk requires the drug to be initiated via an extended and gradual titration course over weeks. Like other anticonvulsants, lamotrigine should be tapered to discontinuation; however, if stopped for more than 5 days, dose titration should be started from the beginning given Stevens-Johnson syndrome risk. Lamotrigine levels are highly influenced by pharmacokinetic interactions, with levels notably increased by valproate and decreased by concomitant carbamazepine or oral contraceptive medications.

Gabapentin and Pregabalin

Gabapentin and pregabalin are extensively used in pain medicine and increasingly as an opioid adjuvant for postoperative pain. With a molecular structure similar to that of GABA, **gabapentin** and **pregabalin** are anticonvulsant calcium channel subunit blocking drugs that decrease synaptic glutamate release. They are not active at the GABA receptor as previously supposed. Both are FDA approved for treatment of epilepsy and neuropathic pain, and pregabalin is additionally FDA approved for the treatment of generalized anxiety disorder. Gabapentin is perhaps the more commonly used in psychiatry, typically for off-label applications including as a sedative and anxiolytic intervention and for treatment of alcohol use disorder and restless legs. Both drugs are relatively safe across a broad range of dosing, although abrupt discontinuation may lead to withdrawal symptoms, and abuse liability in combination with opioids has been documented. There is some added safety due to gabapentin oral absorption that occurs in the duodenum and is increasingly saturated at approximately 1,200 mg.¹⁵⁰ Principle side effects include sedation/lethargy, and, more rarely, peripheral edema may be observed. In rare cases, gabapentin and pregabalin have been associated with rhabdomyolysis, pancreatitis, thrombocytopenia, and neutropenia. The FDA has recently warned about the potential for respiratory suppression when these drugs are used together with opioids or other CNS depressants. Both gabapentin and pregabalin are renally excreted, and caution should be exercised when prescribed in older adults or others with impaired renal clearance. The elimination half-life of both drugs is brief—around 7 hours.

Glutamate Antagonist Drugs

The anesthetic drug **ketamine**, an NMDA glutamate receptor antagonist, is an important adjuvant in the treatment of perioperative and chronic pain.¹⁵¹ Consensus guidelines were released for chronic pain and acute pain in 2018 by the American Society of Regional Anesthesia and Pain Medicine.^{152,153} It has also been explored with great promise in the treatment of depressive mood disorders. Evidence of its robust and rapid effects can be seen in a meta-analysis of seven double-blind placebo-controlled randomized clinical trials incorporating a total of 147 patients.¹⁵⁴ The FDA has approved a racemic ketamine formulation, intranasal **esketamine**, for refractory depression given evidence provided by a phase III trial of separation from placebo in the primary endpoint.¹⁵⁵ At the same time, there are risks associated with ketamine, including abuse potential and potential suicide risk.¹⁵⁵ With chronic, high-frequency ketamine substance abuse, there have been reports of cognitive impairment and cystitis.^{156,157}

The typical dose of ketamine as an adjuvant analgesic is 0.5 to 1 mg/kg per hour. In contrast, the typical antidepressant dose of ketamine hydrochloride, 0.5 mg/kg delivered IV over 40 minutes, does not produce general anesthetic effects (peak plasma concentrations of 70-200 ng/mL are attained compared with 2,000-3,000 ng/mL when used for general anesthesia).¹⁵⁸ The IV ketamine at antidepressant doses is, however, associated with transient increases in systolic and diastolic blood pressure.¹⁵⁹ Ketamine infusions for treatment of chronic pain and depression should only be performed at sites with expertise in this approach,

with appropriate safeguards in place including plans for monitoring side effects and changes in psychiatric symptoms, and for screening individuals who have current or past substance abuse.¹⁶⁰

Other Glutamate Modulators

A number of other glutamate antagonist drugs have been explored for off-label use in obsessive-compulsive disorder and other conditions thought to be associated with hyperactivity of glutamatergic cortico-striato-thalamo-cortical circuits. In addition to ketamine, these drugs include the NMDA antagonist **memantine**, the sodium channel blocking drugs **topiramate** and **riluzole**, and the glutathione precursor **N-acetylcysteine**.¹⁶¹⁻¹⁶⁴ Memantine is FDA approved for treatment of moderate to severe Alzheimer disease, where it is hypothesized to confer benefit by reducing glutamate-mediated neuronal exitotoxicity. Additional off-label applications have included fibromyalgia, neuropathic, and other types of chronic pain; although high-quality evidence for benefit in these off-label uses is limited, its minimal side effect profile has supported ongoing interest.¹⁶⁵ Topiramate is additionally used off-label for alcohol use disorder and antipsychotic-associated weight gain, and N-acetylcysteine has evidence supporting efficacy in schizophrenia.¹⁶⁶⁻¹⁶⁸ There are minimal risks or drug interactions associated with use of memantine or N-acetylcysteine. Topiramate is a weak carbonic anhydrase inhibitor and as such is associated with nephrolithiasis and may increase risk of hypohidrosis and hyperthermia. Riluzole has been associated with hepatitis, pancreatitis, and rare instance of bone marrow suppression, and in overdose may be associated with methemoglobinemia.

Drugs With Primarily Acetylcholinergic Action

Anticholinergic effects of psychopharmacologic drugs are a common cause of adverse effects and drug-related morbidity, reflecting both peripheral actions (eg, orthostasis, urinary retention) and central actions (eg, cognitive impairment, delirium) that are familiar to the anesthesiologist. A number of procholinergic drugs, however, have utility as psychopharmacologic agents, reflecting the actions of acetylcholine on cortical and subcortical circuits related to cognition, memory, and reward.

Acetylcholinesterase Inhibitors

Donepezil and **rivastigmine** are acetylcholinesterase inhibitors that are approved for treatment of cognitive deficits in mild to moderate Alzheimer dementia. Rivastigmine additionally is FDA approved for use in dementia related to Parkinson disease. Possible adverse effects of the acetylcholinesterase inhibitors include gastrointestinal disturbances (nausea, vomiting, diarrhea), anorexia with weight loss, sweating, muscle cramps, weakness, and nightmares. Given potential for adverse effects, both medications are typically titrated gradually to target dose. A transdermal patch formulation of rivastigmine may allow for decreased frequency of gastrointestinal side effects.¹⁶⁹

Anesthetic Considerations

Importantly, acetylcholinesterase inhibitors may prolong the effects of depolarizing neuromuscular blockade or reverse or decrease the effects of nondepolarizing neuromuscular blockers.^{170,171} This has led to suggestions that these medications be discontinued prior to elective surgeries or that nondepolarizing agents be used in emergency surgeries for patients currently taking acetylcholinesterase inhibitors.¹⁷² This is of questionable relevance if best practices are followed and the nondepolarizing muscle relaxant is titrated to effect with a peripheral nerve stimulator. As with all medications, the benefits of discontinuation need to be balanced against the risks.

The half-life of donepezil is long—at approximately 70 hours—and as such, prolonged washout over 2 weeks may be required prior to elective procedures. Rivastigmine, in contrast, has a short half-life of 3 to 4 hours and can be discontinued the day prior to surgery. The acetylcholinesterase inhibitors have also been associated in case reports with bradycardia and hypotension and may rarely contribute to QTc prolongation and arrhythmia risk.¹⁷³

Acetylcholine Receptor Agonist and Multimodal Drugs

Galantamine, like rivastigmine and donepezil, is a competitive acetylcholinesterase inhibitor; yet, it also acts as an agonist at nicotinic acetylcholine receptors, and as such, it is considered an acetylcholine multimodal drug. It is FDA approved for treatment of cognitive impairment in dementia related to Alzheimer disease, and its benefit is thought to reflect both direct agonist and enzyme inhibitor effects. As with the other acetylcholinesterase inhibitors, gastrointestinal adverse effects are notable upon initiation of the drug, the potential for increased bradycardia and arrhythmia risk should be considered, and it is recommended to be discontinued prior to anesthesia. Due to impacts on neuromuscular blockade, it was even used as a reversal agent in the early 1960s.^{174–176} Like rivastigmine, its half-life is short—at 7 hours—and it can be stopped 1 to 2 days prior to anesthesia.

Varenicline is a partial agonist at multiple nicotinic acetylcholine receptors, with effects most prominently at $\alpha_4\beta_2$ receptors, where it blocks and limits nicotine-driven reward signaling in the mesolimbic dopamine circuits. In this way, it decreases craving for nicotine products and limits nicotine withdrawal symptoms. As such, it is FDA approved for smoking cessation and considered the most effective medication intervention for smoking cessation.¹⁷⁷ The most commonly associated adverse effect is mild nausea. In the initial postmarketing period, concerns were raised about potential neuropsychiatric or cardiovascular risks associated with varenicline, yet a large postmarketing cohort study did not find evidence for increased risk of either neuropsychiatric or cardiac adverse events.¹⁷⁸ There are no reports of varenicline interfering with safe administration of anesthesia, and varenicline has been found beneficial as a component of perioperative smoking cessation interventions.^{179,180}

Drugs With Primarily γ -Aminobutyric Acid (GABA)-ergic Action

Benzodiazepines

Benzodiazepines (see [Chapter 5](#)) are used clinically as short-term anxiolytics, sedatives, anticonvulsants, and muscle relaxants. They appear to produce all these effects by facilitating the actions of GABA, the major inhibitory neurotransmitter in the nervous system. Short-acting benzodiazepines are used for anxiolysis in many if not most general anesthetics. The immediate effectiveness of benzodiazepines, combined with the high frequency of anxiety and insomnia in the adult population, has led to these drugs being widely prescribed. However, reflecting the superiority of SSRIs for first-line pharmacologic treatment of anxiety disorders, and given potential for tolerance, physiologic dependency, and iatrogenic anxiety related to withdrawal, abuse liability, risks related to intoxication (eg, falls and motor vehicle accidents), and risks of overdose and respiratory suppression—particularly when used in conjunction with opioid medications—benzodiazepines are increasingly avoided by psychiatrists, or prescribed only for time-limited periods of intermittent use.

When benzodiazepines are used, low doses (eg, **clonazepam** 0.5 mg, 1-3 times daily) are typically selected to minimize sedation. A total daily dose of greater than 3 mg **lorazepam** or its equivalent is almost never needed and may signal further evaluation due to the potential for substance abuse. A history of alcohol abuse or substance abuse is a relative contraindication to use of benzodiazepines for treatment of anxiety. Problems with benzodiazepine rebound and withdrawal symptoms can be minimized if low-potency, long-acting drugs are used. Elderly patients manifest greater sedation and greater impairment of psychomotor performance than younger persons receiving the same dose, and benzodiazepine use is thus relatively contraindicated in the elderly.

Other GABA_A Receptor Modulators

The “z-drugs” **zolpidem**, **zopiclone**, **eszopiclone**, and **zaleplon**, like the benzodiazepines, are positive allosteric modulators of the GABA_A receptor and are licensed for short-term use as sleep-promoting drugs. The drugs differ primarily by their typically short half-lives. These drugs may have less potential for tolerance and dependency than the benzodiazepines; however, abrupt discontinuation after prolonged and high-dose use has been associated with benzodiazepine-like withdrawal phenomena. Use of this medication class has been associated with abnormal sleep behaviors. Inhibitors of CYP450 enzymes 3A4 and 1A2 may

increase levels of zolpidem, the most commonly used of this class, and women are known to metabolize zolpidem more slowly than men, for which reason lower starting doses are recommended for women.

Lithium

Lithium salts have been studied in the treatment of mood disorders since the 1890s.¹⁸¹ In addition to the antimanic and relapse-preventative effects of lithium in bipolar disorder, lithium is an evidence-based adjunctive treatment in treatment-resistant major depressive disorder and is one of only a few drugs shown to decrease risk of suicide.¹⁸² Lithium's narrow therapeutic index, significant potential for toxicity, and potential for drug interactions are discussed in detail in the following text.

Mechanisms of Action

Lithium has many neurobiologic effects, but the basis for lithium's efficacy in bipolar disorder has long been unclear.¹⁸³ Contemporary models invoke lithium's influence on multiple neurochemical pathways, including increases in serotonin production and presynaptic release and decreases in glutamatergic neurotransmission. Lithium modulates a number of intracellular signaling cascades, causing reduction in amplitude of Gi and Gs signaling cascades, decreases in inositol signaling, and modulating other enzymes requiring magnesium as a cofactor, including GSK3 β and β -arrestin. These in turn may modulate pathways leading to neurotrophic effects or to influence on chronobiologic systems.¹⁸⁴

Dosage and Monitoring

Safe and effective use of lithium can be achieved only by monitoring plasma concentrations. Oral doses of lithium chloride typically range from 600 to 1,800 mg daily in divided doses; yet, dosing is always based on target serum level. For maintenance treatment of bipolar disorder, consensus guidelines suggest a plasma level of 0.6 to 0.8 mEq/L, although lower levels may be used in unipolar depression.¹⁸⁵ For treatment of acute mania, levels between 1.0 and 1.2 mEq/L may be targeted. Because the elimination half-time is about 24 hours, plasma concentrations should be measured no sooner than 5 days after a change in dosage, unless toxicity is suspected. In elderly patients and in patients with renal disease, the elimination half-time for lithium is prolonged; the time to equilibration can be delayed to 7 days or longer. If toxicity is suspected, lithium should be withheld and the plasma concentration determined immediately, taking into account the time that has elapsed since the last dose.

Adverse Effects

Lithium-treated patients may experience a number of potential side effects, all considered dose dependent. Mild side effects include fine motor tremor, typically resolving with dose reduction, but tremor present at lower doses when lithium is combined with bupropion or other SRIs or norepinephrine reuptake inhibitors. If necessary, β -adrenergic antagonists may mitigate tremor. Clinically important dermatologic toxicities of lithium include cystic acne and exacerbations of psoriasis. Lithium also may cause gastric irritation, typically managed by nighttime-only dosing or use of an extended-release formulation.

Renal Effects

The most common serious side effects of lithium occur at the kidneys. Acutely, within weeks of initiating lithium treatment, approximately 50% of patients will demonstrate polyuria to some degree. Approximately 20% of these may develop nephrogenic diabetes insipidus, with possible effects including hypovolemia, hypernatremia, hyperchloremic metabolic acidosis, and distal renal tubular acidosis.¹⁸⁶ These changes are thought to be due to intracellular signaling changes resulting in downregulation of aquaporin-2 in the collecting duct. With chronic exposure to high lithium doses over years or decades, chronic kidney disease may develop characterized by nephrogenic diabetes insipidus, proteinuria, and histologic changes consistent with tubulointerstitial nephritis. The potassium-sparing diuretic amiloride is effective in decreasing urine volume without affecting the plasma concentrations of either lithium or potassium, although it is unclear whether this diuretic may prevent chronic kidney disease.¹⁸⁷ It is recommended that renal function be evaluated by measuring blood urea nitrogen or plasma creatinine every 6 months.

Cardiac Effects

Cardiac effects of lithium treatment may include changes on the ECG characterized by T-wave flattening or inversion, yet there seem to be no related clinical effects. The ECG changes are reversible within 2 weeks when lithium is discontinued. Clinically significant lithium-induced cardiac conduction disturbances are rare, although sinoatrial node dysfunction and sinoatrial node block have been described. Patients with preexisting sinoatrial node dysfunction (sick sinus syndrome) should probably be treated with lithium only if they have an artificial cardiac pacemaker in place.

Endocrine Effects

Hypothyroidism develops in about 5% of patients treated with lithium and is more common in women than men. For this reason, it is recommended that thyroid-stimulating hormone levels be measured every 6 months, along with lithium level, electrolytes, and blood urea nitrogen/creatinine. If necessary, levothyroxine therapy may be initiated without discontinuing lithium. Provided no autoimmune or other cause of hypothyroidism is present, thyroid status may be expected to normalize if and when lithium is discontinued.

Drug Interactions

Lithium may interact pharmacodynamically or pharmacokinetically with many classes of medication ([Table 43.7](#)). Rarely, lithium may cause or potentiate extrapyramidal effects of dopamine antagonist medications, and, in case literature, lithium has been associated with neuroleptic malignant syndrome. Similarly, given potential to increase serotonergic neurotransmission, lithium may cause serotonin syndrome when added to SSRIs or MAOIs; however, its use together with SSRIs or MAOIs is not generally contraindicated.

TABLE 43.7

Drug interactions with lithium

Drug	Interaction
Thiazide diuretics	Increased plasma lithium concentration as a result of decreased renal clearance
Furosemide	Usually no change in the plasma lithium concentration
Nonsteroidal antiinflammatory drugs	Increased plasma lithium concentration as a result of decreased renal clearance (exceptions are aspirin and sulindac)
Aminophylline	Decreased plasma lithium concentration as result of increased renal clearance
Angiotensin-converting enzyme inhibitors	May increase plasma lithium concentration
Dopamine antagonist drugs	Lithium may exacerbate EPS or increase the risk of the neuroleptic malignant syndrome.
Anticonvulsant drugs (carbamazepine)	Concurrent use with lithium may result in additive neurotoxicity
β-Adrenergic antagonists	Decrease lithium-induced tremor
Neuromuscular blocking drugs	Lithium may prolong the duration of action.

Adapted from Price LH, Heninger GR. Lithium in the treatment of mood disorders. *N Engl J Med.* 1994;331(9):591-598.

Diuretic drugs may significantly influence lithium levels. Lithium is distributed throughout the total body water and is excreted almost entirely by the kidneys. Lithium, like sodium, is filtered by the glomerulus and reabsorbed by the proximal, but not distal, renal tubules. Thus, its renal excretion is not enhanced by thiazide diuretics, which act selectively on the distal renal tubules. In fact, because proximal reabsorption of lithium and sodium is competitive, depletion of sodium as produced by dehydration, decreased sodium intake, and thiazide and loop diuretics may increase reabsorption of lithium by proximal renal tubules, resulting in as much as a 50% increase in the plasma concentration of lithium. Potassium-sparing diuretics (triamterene, spironolactone) do not facilitate reabsorption of lithium and, in fact, may increase excretion.

Nonsteroidal antiinflammatory drugs, by altering renal blood flow, may produce marked increases in the plasma concentration of lithium and should be used with care.

Anesthetic Considerations

The association of sedation with lithium therapy suggests that anesthetic requirements for injected and inhaled drugs could be decreased. High plasma concentrations of lithium may delay recovery from the CNS depressant effects of barbiturates.¹⁸⁸ Responses to depolarizing and nondepolarizing neuromuscular blocking drugs may be prolonged in the presence of lithium.¹⁸⁹

Toxicity

Lithium toxicity may present acutely, as a consequence of overdose, or may be chronic. Diuretic therapy, nonsteroidal antiinflammatory drugs, sodium restriction, and sodium wasting may increase reabsorption of lithium and thus increase plasma lithium concentrations.

Many symptoms and signs of toxicity are closely correlated with the plasma lithium concentration (**Table 43.8**).¹⁸³ Mild lithium toxicity is reflected by sedation, nausea, skeletal muscle weakness, and changes on the ECG characterized by widening of the QRS complex. Atrioventricular heart block, hypotension, cardiac dysrhythmias, and seizures may occur when plasma concentrations of lithium are greater than 2 mEq/L. Significant lithium toxicity is a medical emergency that may require aggressive treatment, including hemodialysis. Monitoring for rebound in lithium levels after hemodialysis is essential, as absorption may continue from gastrointestinal contents and lithium may equilibrate slowly between intra- and extracellular stores.¹⁹⁰ If renal function is adequate, excretion of lithium ions can be modestly accelerated by osmotic diuresis and IV administration of sodium bicarbonate.

TABLE 43.8

Signs and symptoms of lithium toxicity

		Toxic effects	Plasma lithium concentration (mEq/L)	Signs and symptoms
Mild	1.0–1.5			Lethargy Irritability Skeletal muscle weakness Tremor Slurred speech Nausea
Moderate	1.6–2.5			Confusion Drowsiness Restlessness Unsteady gait Coarse tremor Dysarthria Skeletal muscle fasciculations Vomiting
Severe	>2.5			Impaired consciousness (coma) Delirium Ataxia Extrapyramidal symptoms Seizures Impaired renal function

Adapted from Price LH, Heninger GR. Lithium in the treatment of mood disorders. *N Engl J Med.* 1994;331(9):591-598.

Cannabinoids

Cannabis is an alkaloid mixture of more than 400 compounds derived from the cannabis sativa plant. Cannabis has been used for thousands of years and is presently the most commonly used illicit drug in the world. The most abundant cannabinoids are δ -9-tetrahydrocannabinol (D9THC), cannabidiol, and cannabinol.¹⁹¹ The D9THC is the main psychotropically active cannabinoid. Two principal endogenous cannabis receptors (CB_1 and CB_2) have been identified. The CB_1 receptors are present in the CNS (especially spinal cord), and CB_2 receptors are located peripherally and linked with cells in the immune system. Both receptors are members of the G protein family and like opioid receptors exert their actions by modulating second messenger activity (adenylate cyclase activity) and calcium ion function. Endogenous cannabinoid agonists (anandamide, 2-arachidonoylglycerol) have been identified and produce effects similar to D9THC.

Pharmacokinetics

Cannabinoids undergo substantial hepatic first-pass metabolism following oral administration such that only 10% to 20% of the ingested dose reaches the systemic circulation. This metabolism produces large amounts of active metabolite, 11-hydroxy- δ -9-tetrahydrocannabinol, which is as active as the parent compound (D9THC) and has a prolonged half-time. The peak clinical effect after oral administration occurs after 1 to 2 hours and duration of action is 4 to 6 hours. In contrast, inhalation administration results in onset of action within seconds.

Toxicity

Euphoria and feelings of relaxation occur at plasma cannabinoid concentrations of about 3 ng/mL, and this can be produced by 2 to 3 mg of D9THC. Acute intoxication may cause perceptual alterations, distortion of time, intensification of normal sensory experiences, decreased reaction times, poor motor skills, increased appetite, impairment of skilled activities, tachycardia, and hypotension. The greatest concern is the creation of long-term toxicity, development of physical dependence associated with withdrawal symptom during a period of abstinence after frequent use.¹⁹² Cannabis is often mixed with tobacco to make it burn more efficiently. Materials that are present in cannabis smoke are carcinogenic. Chronic inhalation of cannabis smoke is associated with an increased incidence of chronic obstructive lung disease and carcinoma of the lung and larynx. Persistent use of cannabis may be associated with decreased reproductive potential and reduced production of testosterone.

Clinical Uses

The D9THC is increasingly used for the long-term treatment of nausea, vomiting, cachexia, and management of chronic pain including migraine.¹⁹³ The role of the endogenous cannabinoid system is not fully understood, but evidence suggests it is involved with analgesia, cognition, appetite, vomiting, bronchodilation, inflammation, and immune control.¹⁹¹ Drugs that target the endocannabinoid system have been studied for use in addiction treatment, with a recent study reporting cannabidiol can reduce cue-induced craving and anxiety in drug-abstinent individuals with heroin use disorder.^{194,195} Cannabinoids are highly lipid soluble, and the presence of CB_1 receptors in the spinal cord suggests potential analgesic efficacy if placed in the epidural or intrathecal space. Although use of cannabis for analgesia introduces the potential for psychic and physical dependence, there is considerably less risk of life-threatening side effects compared to those associated with opioids. Pure D9THC may be effective in the treatment of chemotherapy-induced nausea and vomiting and is a recognized appetite stimulant in patients with terminal disease. Relief of skeletal muscle spasms in patients with multiple sclerosis has been described. The use of D9THC may be associated with an increased risk of myocardial infarction and thromboangiitis obliterans, perhaps reflecting D9THC-induced platelet activation.¹⁹³

The CB_1 receptors are principally expressed on neurons, and their activation has been associated with antinociception. The CB_2 receptors are principally expressed on glia and immune cells, and their activation is associated with antiinflammatory activity and reduction in chronic and neuropathic pain. Subtype-specific agonists are under investigation for pain therapy in order to overcome the problem of a narrow therapeutic window seen with non-subtype-selective cannabinoid drugs between pain relief and psychogenic effects.¹⁹⁶

¹⁹⁸ There have been many studies of the use of cannabinoids in chronic noncancer pain that have been of moderate quality and largely inconclusive when considered together. A recent meta-analysis concluded that the number needed to treat is likely high and the number needed to harm is low. Now that recreational use of cannabis is legal in multiple states, it is not uncommon for patients to be affected by cannabis in the perioperative period. A recent retrospective propensity-matched study of patients having major orthopedic surgery found that those on preoperative cannabinoids had higher pain scores at rest and with movement in the early postoperative period. There was also more sleep interruption in patients who were taking cannabinoids preoperatively.¹⁹⁹ As with any retrospective study, causality cannot be inferred. The cannabinoids may have been used to treat preoperative pain.

Conclusion

In conclusion, this thorough review of drugs used for psychopharmacologic therapy needs to be viewed in the context of the statistics mentioned in the second paragraph of this chapter. Nearly 13% of Americans older than age 12 used antidepressant medications in the past month.³ Twenty-four million prescriptions were issued in the United States in 2017 for the six most commonly prescribed antipsychotic drugs.⁴ A large portion of patients that we care for each day—whether you practice ambulatory, cardiac, or regional anesthesia, in the ICU or the pain clinic—will be taking drugs that affect their psychopharmacology. It behooves us to maintain an up-to-date understanding of the pharmacology, physiology, and potential drug interactions and bring this to bear in our practice.

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PART IX Special Populations

Physiology of the Newborn*

Updated by: Becky J. Wong • Lisa Wise-Faberowski

In the absence of inborn metabolic dysfunction or birth trauma, the neonate is able to meet his or her physiologic needs when not under stress. However, neonatal physiology is characterized by decreased functional reserve. Increased physiologic demands may place a significant burden on organ systems that have not yet developed normal adult functional reserve.

Neonatal Physiology

Neonatal oxygen consumption is approximately 6 mL/kg per minute compared to 3 mL/kg per minute in the adult. The high metabolic rate of the neonate is the crucial determinant of cardiopulmonary function. Even under normal physiologic circumstances, the immature cardiac and respiratory systems operate near the edge of their functional reserve to support this metabolic demand. Immaturity of multiple neonatal organ systems creates important developmental differences in drug handling and response when compared to the older child and adults.¹

Neonatal Cardiovascular Physiology

The newborn infant is in a state of transition from the fetal, intrauterine to the newborn, extrauterine circulatory pattern. As described in [Chapter 45](#), the fetal circulation is characterized by high pulmonary vascular resistance, low systemic vascular resistance (including the placenta), and right-to-left cardiac shunting via the foramen ovale and ductus arteriosus. Expansion of the lungs at birth increases PO₂ and causes a rapid decline in pulmonary vascular resistance and an increase in pulmonary blood flow. The decrease in pulmonary vascular resistance at birth is mediated by the endogenous production of nitric oxide. Increasing blood return to the heart via the pulmonary veins raises the pressure of the left atrium above that of the right, causing a functional closure of the foramen ovale. The functional closure of the ductus arteriosus is, in part, mediated by an increase in arterial oxygen partial pressure and is normally complete within the first 10 to 15 hours of life in the term neonate. However, anatomic closure of the foramen ovale usually occurs between 3 months and 1 year of age. The foramen remains anatomically patent in 10% to 30% of people throughout life.² These individuals are described as having a “probe patent” foramen ovale, meaning that a probe or other surgical instrument can be passed through the foramen ovale. In most of these individuals, the foramen is functionally closed by the lack of any significant pressure gradient between the left and right atria; however, in conditions where the pulmonary vascular resistance rises, significant right-to-left shunting can occur. Individuals with a probe patent foramen ovale are also at risk for systemic air embolism and resultant stroke when air emboli pass from the pulmonary to the systemic circulation. Because the foramen ovale and ductus arteriosus are only functionally closed in the neonatal period, the neonatal circulation is able to readily revert to the fetal pattern, particularly in response to physiologic stresses occasionally encountered in the perinatal period. The neonatal pulmonary circulation is very reactive. Hypoxemia, hypercarbia, or acidosis cause both pulmonary vasoconstriction and dilation of the ductus arteriosus. Increases in pulmonary vascular resistance result in right-to-left shunting across the foramen ovale and ductus arteriosus. Right-to-left shunting, by causing arterial hypoxemia, causes a further increase in pulmonary vascular resistance, thus creating a vicious cycle. This “cycle” of persistent pulmonary hypertension may be seen in premature neonates and those with diaphragmatic hernia, meconium aspiration, infection, congenital heart disease, and polycythemia.

The neonatal myocardium contains immature contractile elements and is less compliant than the adult myocardium. The Frank-Starling relationship is functional only within a very narrow range of left ventricular

end diastolic pressure ([Figure 44.1](#)).³ Thus, there is a limited increase in cardiac output to be gained from aggressive volume loading in the normovolemic newborn. However, if preload is reduced by hypovolemia or dehydration, normalization of volume status will generally restore cardiac output. However, because stroke volume cannot be significantly augmented by volume loading, and because contractile reserve is limited, neonatal cardiac output is exquisitely dependent on heart rate.

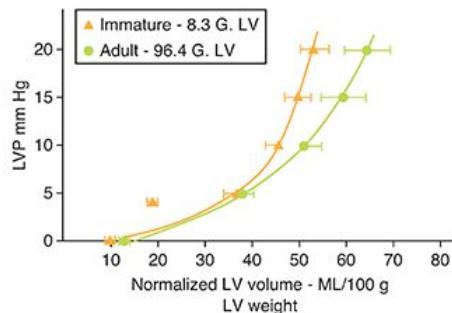


FIGURE 44.1 Pressure-volume curve for neonatal and adult heart. Pressure-volume curves for adult and neonatal canine heart. The immature heart is less compliant than the adult heart. As a result, the pressure-volume curves diverge above a left ventricular pressure (LVP) of about 5 mm Hg.

Although adrenergic receptors are thought to be mature at birth, sympathetic innervation is incomplete. After birth, neurotransmitter concentrations increase progressively, reflecting the maturation of sympathetic innervation. When compared to the adult, neonatal myocardium is more sensitive to norepinephrine.⁴ This phenomenon is a reflection of the relatively denervated status of neonatal myocardium. Dopamine is an indirectly acting inotrope that depends, in part, upon endogenous norepinephrine release for its action. Neonatal myocardium, being deficient in sympathetic innervation, is therefore less responsive to dopamine.

To meet the elevated metabolic demand, neonatal cardiac output, relative to body weight, is twice that of the adult. This is achieved with a relatively rapid heart rate (140 beats per minute) because as described earlier, stroke volume cannot be significantly increased. The neonatal circulation is characterized by centralization (increased peripheral vascular resistance and distribution of cardiac output primarily to vital organs), a situation comparable to an adult in compensated shock. Because neonatal baroreflex activity is impaired, the response to hemorrhage produces little increase in heart rate or change in total peripheral resistance. Thus, even a modest (10%) reduction in blood volume will cause a 15% to 30% decrease in mean blood pressure in the newborn infant. The structural and functional immaturity of the neonatal cardiovascular system severely limits the reserve that is available in the face of common perinatal and perioperative events such as hypovolemia, anesthetic-induced depression of contractility, relative bradycardia and positive pressure ventilation-induced decreases in venous return. The marginal cardiovascular reserve of the neonate and leftward shift of the fetal hemoglobin dissociation curve, decreased oxygen unloading to the tissues, are the rationale underlying the recommendation that the hematocrit be maintained at 30% or higher to prevent tissue ischemia in the newborn.

Respiratory Physiology of the Newborn

The respiratory system of a term neonate at birth is immature and postnatal development continues through early childhood. Although the conducting airways are fully developed by 16 weeks of gestation, the number of alveoli is reduced at birth. A premature infant born at 24 to 28 weeks of gestation is just beginning to develop alveoli from the distal saccules of the lung.⁵ Complete alveolar maturation does not occur until 8 to 10 years of age. At birth, the infant possesses approximately one-tenth of the adult population of alveoli. Thus, the ratio of alveolar surface area to body surface area is one-third that of the adult. To satisfy increased oxygen demand, neonatal alveolar minute ventilation is twice that of the adult. Increasing respiratory rate rather than tidal volume is the most efficient means to increase alveolar ventilation in the newborn. The diaphragm is less efficient in neonates, as it is flatter/less dome-shaped with fewer high-oxidative, less fatigued muscle fibers than in the adult. Ventilation-perfusion imbalance occurs as a result of distal airway

closure, as the closing volume can exceed functional residual capacity (FRC) in neonates. Overall, FRC is lower in the neonate due to the high elastic recoil of the chest wall during normal tidal breathing. This phenomenon is responsible for an increase in the alveolar-arterial oxygen tension gradient compared to adults.

Adequate gas exchange depends on adequate alveolar recruitment and thus surfactant function. Production of surfactant begins by 23 to 24 weeks of gestation and reaches maturity at approximately 35 weeks of gestation. Surfactant-deficient preterm infants have decreased lung compliance and are at risk for the development of respiratory distress syndrome.⁵ Administration of corticosteroids to mothers in preterm labor may accelerate lung maturation in the fetus. Furthermore, the instillation of intratracheal exogenous surfactant in preterm babies has considerably improved the prognosis for premature infants. Infants born to mothers with intrauterine infection have a paradoxical increase in pulmonary maturation. The enhancement in lung maturation can be mimicked with lipopolysaccharide, suggesting that the effect is due to local inflammatory mediators rather than a downstream effect of corticosteroids.⁶ In humans, the effect of inflammation on lung maturation is not enhanced by corticosteroid administration.⁷

The neonatal chest wall is more compliant and has less outward but more inward recoil than that of the adult. Thus, the neonatal lung has a greater tendency to collapse and the infant is obliged to use active mechanisms to maintain normal lung volumes (**Table 44.1**). First, by breathing at a relatively rapid rate, the duration of expiration is limited. In this way, inspiration is initiated before the lung has completed recoiling to its end-expiratory volume. Second, the neonate uses intercostal muscle activity during expiration to stabilize the chest wall, thus retarding the decline in lung volume during expiration. Last, the neonate exhales through a partially closed glottis, also retarding expiratory flow and maintaining end-expiratory lung volume. The awake neonate has an FRC that is similar, when normalized to body weight, to that of an adult. However, because neonatal alveolar ventilation is twice that of an adult, the ratio of alveolar ventilation to FRC in the neonate is twice that of the adult. The high ratio of minute ventilation to FRC causes a much more rapid wash out or wash in of oxygen and anesthetic drugs in response to changes in inspired concentrations.

TABLE 44.1

Active mechanisms used by neonates to maintain lung volume^a

- Rapid respiratory rate—early termination of expiration
- Intercostal muscle activity in expiration—stabilizes compliant chest wall
- Expiration against partially closed glottis—retards expiratory flow

^aSignificantly attenuated by general anesthesia.

The active mechanisms used by the newborn to protect lung volume are exquisitely sensitive to the effects of general anesthesia. Therefore, the neonatal FRC may decrease significantly during anesthesia, particularly during periodic breathing and apnea. The combination of increased oxygen consumption and a reduced ratio of alveolar ventilation to FRC in the newborn explains why apnea and hypoventilation are associated with marked and rapid arterial oxygen desaturation.

Although the peripheral chemoreceptors are active from 28 weeks of gestation, their function is immature until several days after birth. Therefore, the neonate and preterm infant exhibit an altered response to hypoxia and hypercarbia. When challenged with hypoxic inspired gas mixtures, both the term and preterm infant have an initial 1- or 2-minute period of hyperventilation followed by sustained hypoventilation. As postnatal age increases, the hyperventilatory response becomes sustained. However, this protective response develops more slowly in the preterm infant and the ventilatory response to hypercarbia is impaired. The impaired neonatal ventilatory responses to hypoxia and hypercarbia are contributing factors to the development of life-threatening apnea and hypoventilation in the postoperative period.⁸ Nasal continuous positive airway pressure and high-flow nasal cannula are two methods for ventilatory support after extubation in the neonatal period. However, in very premature neonates, less than or equal to 1,250 g, the increased fraction of inspired oxygen with high-flow nasal cannula may promote respiratory pauses post extubation.⁹ Although airway resistance is relatively low in infants, in absolute terms, the airways are very narrow.

Relatively minor quantities of secretions or trivial inflammatory disease can produce serious respiratory embarrassment in small infants.

Neonatal Thermoregulation

The neonate tends to become hypothermic during general anesthesia much more rapidly than the adult. Accelerated heat loss in the neonate is related to its relatively large surface area compared to body mass, thinner layer of insulating subcutaneous fat, and a limited capability for thermogenesis. The neonate primarily relies on nonshivering or chemical thermogenesis in brown adipose tissue for heat production. Thermogenesis in brown fat is mediated by the sympathetic nervous system and is stimulated by norepinephrine, resulting in triglyceride hydrolysis. The thermoregulatory range is the ambient temperature range within which an unclothed subject can maintain normal body temperature. The lower limit of the thermoregulatory range (ambient temperature at which core temperature can be maintained) is 1.25°C for an adult but is as high as 23°C and 28°C for the full-term infant and premature infant, respectively.

Therefore, the thermoregulatory range of the neonate is much narrower than that of the adult. During anesthesia and surgery, heat loss in the pediatric patient is further enhanced by decrease in the thermoregulatory threshold due to anesthesia, low ambient temperatures of the operating suite (20°C-22°C), preparation of skin with cold solutions, infusion of cold solutions, anesthesia-induced vasodilatation, and use of dry anesthetic gases in high-flow, nonrebreathing systems. Intraoperative hypothermia will markedly delay emergence. Furthermore, with the return of the thermostatic reflexes, oxygen consumption increases by three- to fourfold as the metabolic rate is increased in an attempt to generate heat. This additional demand on an immature cardiorespiratory system that is already compromised due to the residual effects of anesthesia and surgery may precipitate cardiorespiratory failure.

The loss of heat during anesthesia and surgery can be prevented by a number of simple measures, such as raising operating room temperature to 28°C to 30°C, radiant heat lamps, wrapping the head and extremities with insulating material, using nonvolatile warmed solutions for skin preparation, and administration of warmed intravenous fluids and blood products. Inhaled gases should be heated and humidified. Forced air warming devices are also effective in maintaining perioperative normothermia in neonates.

Neonatal Fluid, Electrolyte, and Renal Physiology

The neonate is characterized by an increased total body water (70% vs 55% in adults), increased extracellular fluid volume, increased water turnover rate, and reduced glomerular filtration rate. The neonatal renal tubules have a decreased ability to absorb sodium, bicarbonate, glucose, amino acids, and phosphates. Neonates are obligate sodium wasters and require sodium supplementation. All of these factors contribute to the potential for overhydration, dehydration, metabolic acidosis, and hyponatremia, necessitating meticulous attention to intraoperative fluid therapy. Compared to adult levels, the glomerular filtration rate in term neonates is only 35% and increases to 90% by the end of infancy.¹⁰ Although third-space translocation of fluids is relatively similar in neonates and adults, neonatal insensible losses vary greatly. Fever, radiant warmers, phototherapy, increased ambient temperature, and decreased humidity all increase insensible loss.

Neonatal Neurophysiology

Electroencephalogram rhythms that are mediated by subcortical integration of cortical and subcortical processes are present from 20 weeks' gestation.¹¹ Somatosensory evoked potentials can be recorded from the fetal cerebral cortex at 29 weeks' gestation.¹² As such, the functional circuitry required for sensation of pain is likely to be present between 20 and 30 weeks' gestation. The neonatal brain is comparatively large at birth compared to the adult. Myelination is incomplete at birth and is typically accomplished before the third year of age.

Although myelination is incomplete, and nerve conduction velocity may be diminished, the shorter conduction distances found in the neonate facilitate rapid transmission of nociceptive impulses to the brain.¹³ As in adults, most nociceptive impulses are transmitted by unmyelinated C fibers and by poorly myelinated A δ fibers. Painful stimuli produce withdrawal, autonomic stimulation, and neuroendocrine stress responses. The concept of plasticity of the nervous system has important implications for the management of pain in

newborns. The failure to provide analgesia for neonates leads to changes in nociceptive pathways in the dorsal horn of the spinal cord and in the brain. As a result, future painful insults result in exaggerated pain perception. Indeed, in human newborns, the failure to provide adequate anesthesia or analgesia for circumcision is associated with long-term changes, including an increased response to immunization later in childhood.¹⁴

The adequate treatment of pain in the neonatal period is challenging because of the fear of respiratory depression associated with opioid administration. Fortunately, several nonpharmacologic behavioral interventions have analgesic effects in infants.¹⁵ Analgesia may be induced by the administration of sucrose and by suckling. These effects are mediated via descending endogenous opioid and nonopioid mechanisms originating in the brainstem and may be partially reversed by the administration of naloxone.¹⁶

The germinal matrix has a rich blood supply, thin vessel walls, and scant vascular supporting tissue, causing the vessels of this region to be susceptible to rupture. With increasing gestational age, the germinal matrix involutes and is absent in the full-term infant. Intraventricular hemorrhage in the premature infant and in the fetus originates predominantly in the germinal matrix and occasionally in the choroid plexus. Periventricular-intraventricular hemorrhage occurs in 40% to 50% of premature infants and is a major cause of neonatal morbidity and mortality. The factors in the pathogenesis of intraventricular hemorrhage include abrupt changes in cerebral hemodynamics, changes in intracranial pressure, disturbances in osmotic equilibrium, and coagulopathy.

Preterm infants are also at risk for retinopathy of prematurity in which abnormal growth of retinal vessels can lead to scarring and blindness. Although gestational age is the primary etiologic factor in the development of retinopathy of prematurity, hyperoxia, hypocarbia, vitamin E deficiency, and acidemia have also been implicated as contributing factors.

Neonatal Hepatic Physiology

Liver functions can be classified into three main categories: metabolism, detoxification, and bile synthesis. Neonates have decreased glycogen stores and are prone to hypoglycemia after relatively brief periods of starvation. The preterm infant is at even greater risk for hypoglycemia. Glucose is therefore an essential element of the intraoperative fluid plan. The term neonate requires 3 to 5 mg/kg per minute and preterm neonates 5 to 6 mg/kg per minute of glucose to maintain serum glucose between 35 and 125 mg/dL.

Bilirubin is a by-product of hemoglobin catabolism in the neonate. Hepatic enzyme uridine diphosphate glucuronyl transferase catalyzes the conjugation of bilirubin with glucuronide. Levels of hepatic uridine diphosphate glucuronyl transferase reaches adult levels during the first few weeks of life.¹⁷ Hyperbilirubinemia and physiologic jaundice is common in the 2-week-old neonate and is multifactorial: increased bilirubin production, deficient conjugation, increased reabsorption of unconjugated bilirubin via the enterohepatic circulation, and insufficient oral intake.¹⁸ The hyperbilirubinemia is exaggerated in the preterm neonate compared to the term neonate.

Pharmacology and drug metabolism in neonates are not extensively studied as drug companies often classify neonates as an at-risk population and exclude them from their studies. Therefore, many drugs are considered off-label use in neonates. In light of this, the clinician should be cognizant of the neonate's renal and liver maturation, along with the metabolism of certain drugs, which may not reach normal adult levels until around 6 months of age.¹⁹

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Maternal and Fetal Physiology and Pharmacology

Amy W. Willett • Pamela Flood

Introduction

As many as 1 out of every 50 pregnant women will undergo some type of surgery during their pregnancy. This rate is likely to increase with increasing indications and improved outcomes from fetal interventions. There are currently no data-driven recommendations best practices for anesthesia for nonobstetric surgery during pregnancy given the barriers to conducting large-scale randomized clinical trials. Thus, it is critical for the anesthesiologist to be an expert on maternal physiology and pharmacology to optimize intraoperative maternal-fetal well-being in multiple clinical scenarios.

Pregnancy causes significant physiologic changes that provide for the metabolic demands of the growing fetus. The pharmacokinetics and pharmacodynamics of many drugs are altered during pregnancy. When possible, surgery is performed during the second trimester of pregnancy to avoid affecting major organogenesis during the first trimester and to reduce the risk of preterm delivery that is increased in the third trimester. The immediate effects of anesthesia are normally well tolerated by the fetus. The fetus does not depend on alveolar ventilation for oxygenation or carbon dioxide removal and has the maternal organs to help manage drug metabolism and excretion. However, the fetal cardiac output is sensitive to depression by anesthetic drugs. Drugs used in anesthesia cross the placenta to a variable extent (**Table 45.1A–G**).^{1–82}

TABLE 45.1A

Antihypertensive drugs^a

Drug	Dose adjustment	F/M ratio	Breast milk/maternal plasma ratio	Former FDA category	PK/PD alteration
Atenolol	No change in dose required	0.94	1.6-6.8	D	Increased oral absorption compensates for increased renal clearance Unchanged $t_{1/2}$ 100% renally cleared
Clonidine	Increased dose/shorter dosing interval may be needed	1.0	1.5	C	Renal clearance increased 2 times $t_{1/2}$ significantly decreased
Diltiazem	Unknown	Unknown	1	C	Unknown
Furosemide	No change in dose required	~1	Excreted in breast milk	C	Clearance unchanged in third trimester
Hydralazine	Unknown	0.72	Small amount of active compound in breast milk	C	Unknown
Labetalol	Increased dose or more frequent dosing	0.4-0.8	0.8-2.6	C	Oral labetalol, clearance increased with advancing pregnancy (1.4 times at 12 weeks, 1.6 times at term) Due to increased activity of hepatic blood flow and induction of UGT1A1
Methyldopa	Unknown	1.2	0.19-0.34	B	Unknown
Metoprolol	Increased dose or more frequent dosing	1	3	C	Oral clearance 4 times greater in third trimester Peak serum concentrations 12%-55% Mechanism increased hepatic blood flow and CYP2D6 induction More effective at lower plasma concentrations in pregnancy
Nifedipine	Increased dose/shorter dosing interval	Unknown	<0.05	C	Oral clearance 4 times higher $t_{1/2}$ decreased by 50% Mechanism increased hepatic blood flow and CYP3A4 induction
Sotalol	Unknown	1.1	>1	B	Unknown

Abbreviations: FDA, U.S. Food and Drug Administration; F/M, fetal/maternal; PK/PD, pharmacokinetic/pharmacodynamics.

^aData from Ansari J, Carvalho B, Shafer SL, Flood P. Pharmacokinetics and Pharmacodynamics of Drugs Commonly Used in Pregnancy and Parturition. *Anesth Analg.* 2016;122(3):786-804.

TABLE 45.1B

Anticoagulants and antiplatelet drugs^a

Drug	Dose adjustment	F/M ratio	Breast milk/maternal plasma ratio	Former FDA category	PK/PD alteration
Acetylsalicylic acid	Unknown, possibly increased dose requirement based on PK	1 for salicylic acid, lower for acetylsalicylic acid due to placental esterases	Peak levels 9-12 hours after dose	N	Slower uptake, lower peak plasma concentration after single dose
Argatroban	Unknown	Unknown, low molecular weight, moderate protein binding Likely crosses placenta	Unknown, low molecular weight, moderate protein binding Likely crosses into breast milk	B	Unknown
Clopidogrel	Unknown	Unknown likely crosses placenta, low molecular weight	Unknown likely crosses into breast milk, low molecular weight	B	Unknown
Dabigatran	Unknown	0.33	Unknown	C	Unknown
Enoxaparin	Must titrate to Xa levels given wide swings in pharmacokinetics through pregnancy; once-daily dosing is likely insufficient given higher clearance.	Does not readily cross placenta due to large molecular weight	Very little excreted into breast milk due to high molecular weight; milk/plasma ratio of <0.025-0.224; also not absorbed orally	B	Increased clearance; larger volume of distribution with major increase in last 2 months of pregnancy Progressive reduction in anti-Xa activity during pregnancy
Fondaparinux	Unknown	0.1 large molecular weight	Unknown	B	Potentially unchanged, case report data
Heparin	Higher doses and/or more frequent intervals aPTT is not valid in pregnancy, measure Xa levels	Does not cross placenta due to large molecular weight	Not excreted into breast milk due to high molecular weight	C	Peak plasma concentration 50% that of nonpregnant controls Reduced efficacy in pregnancy ACCP recommends 10,000 U every 12 hours or monitoring anti-Xa levels
Rivaroxaban	Unknown	Unknown	Manufacturer reports rivaroxaban is excreted in breast milk.	C	Unknown
Warfarin	Highly variable	0.15—not metabolized readily by fetal liver leading to higher INR in fetus	Not excreted into breast milk	X (D if mechanical heart valve)	PK unknown; postpartum patients require more drug than nonpregnant women to achieve therapeutic anticoagulation.

Abbreviations: ACCP, American College of Chest Physicians; aPTT, activated partial thromboplastin time; FDA, U.S. Food and Drug Administration; F/M, fetal/maternal; INR, international normalized ratio; PK/PD, pharmacokinetic/pharmacodynamics.

^aFrom Ansari J, Carvalho B, Shafer SL, Flood P. Pharmacokinetics and pharmacodynamics of drugs commonly used in pregnancy and parturition. *Anesth Analg*. 2016;122(3):786-804. doi:10.1213/ANE.0000000000001143. Review, with permission.

TABLE 45.1C

Opioids^a

Drug	Dose adjustment	F/M ratio	Breast milk/maternal plasma ratio	Former FDA category	PK/PD alteration
Alfentanil	No major dosing changes anticipated	0.3	Excreted into breast milk at low concentrations	C	No change in volume of distribution or clearance
Buprenorphine	Dose increase in third trimester; decreased risk of neonatal withdrawal compared with methadone (adjusted odds ratio; 2.55)	Minimal data; estimated F/M ratio was 6.3 in 1 patient	More data needed; known to cross into breast milk; values not reported; poor oral bioavailability makes absorption during breast-feeding low.	C	Increased metabolism to inactive metabolites via induction of CYP3A4
Codeine	Should not be used because of variable metabolism and excretion into breast milk	See morphine.	See morphine.	C	Prodrug metabolized by CYP2D6 that is induced in pregnancy and has extensive genetic variability
Fentanyl	Unknown	0.5-0.9	1.4-3; low oral bioavailability in neonate	C	Peak maternal concentration 0.5 ng/mL with epidural dosing
Hydrocodone	Unknown; more research needed	Unknown	Fully breastfed neonates received 1.6%-3.7% (range, 0.2%-9%) of the maternal weight-adjusted hydrocodone dose.	C	Increased activity of hepatic CYP2D6 enzyme increases conversion to the more potent opiate, hydromorphone; can result in higher and more rapid peak effect
Hydromorphone	Unknown	Unknown	2.6. Estimated infant dose was 0.67% of the mother's weight-adjusted dose	C	Metabolized by CYP2D6
Meperidine	No change, caution with repeat dosing in breastfeeding	35-106	0.8-1.6. Long $t_{1/2}$ of meperidine and normeperidine in infants—no >1 dose is recommended in breastfeeding women	C	Increased metabolism (inactivation) is expected via induction of CYP3A4 in pregnancy; likely counterbalanced by decreased clearance; no change in $t_{1/2}$
Methadone	Higher dose and shorter dosing interval required. Mean increased dose of 24 mg in methadone maintenance by third trimester, and many authors recommend splitting total daily dose into twice a day. Dose returns to normal by 6 weeks postpartum.	0.2. Withdrawal symptoms occur in 60%-90% of the infants exposed in utero to methadone.	Average = 0.8, wide range of 0.05-1.2. Concentration in breast milk can help with symptoms neonatal abstinence syndrome.	C	Increased clearance; largely due to induction of CYP3A4 and CYP2B6; placental aromatase CYP19 also metabolizes methadone; reduced elimination half-life of 8-20 hours compared with the 24-hour half-life in a nonpregnant patient
Morphine	May require increased dose and/or increased dosing interval	0.61-1; undetectable in most infants 1-2 hour after a single IV maternal dose	<1; low oral bioavailability (26%) in infant; receives 8%-12% maternal dose	C	Volume of distribution unchanged, clearance >70%, decreased half-life, glucuronide conjugation by UGT
Oxycodone	May require a shorter dosing interval due to faster elimination half time	Maternal plasma/umbilical plasma ration of 1	3.2	B	Increased clearance via increased GFR as well as induction of CYP3A4 and CYP2D6 induction; shorter elimination half time in laboring

					women (decreased from 3.8 to 2.6 hours)
Remifentanil	May require higher dose to achieve the same plasma concentration due to increased clearance	0.29-0.88; extensive fetal and placental metabolism occurs, as evidenced by a large decrease from the UV; MA ratio of 0.88	Unknown; low molecular weight and high lipid solubility suggest that it will be excreted into breast milk	C	Clearance more than doubles, likely due to larger blood plasma volume, increased cardiac output, and increased renal blood flow

Abbreviations: FDA, U.S. Food and Drug Administration; F/M, fetal/maternal; GFR, glomerular filtration rate; IV, intravenous; MA, maternal artery; PK/PD, pharmacokinetic/pharmacodynamics; UGT, glucuronosyltransferase; UV, umbilical vein.

^aFrom Ansari J, Carvalho B, Shafer SL, Flood P. Pharmacokinetics and pharmacodynamics of drugs commonly used in pregnancy and parturition. *Anesth Analg*. 2016;122(3):786-804.
doi:10.1213/ANE.0000000000001143. Review, with permission.

TABLE 45.1D

Sedative hypnotic drugs^a

Drug	Dose adjustment	F/M ratio	Breast milk/maternal plasma ratio	Former FDA category	PK/PD alteration
Diazepam	Not recommended	1	0.2-2	D	No change in clearance
Etomidate	Unknown	0.5-0.86	1.2; undetectable in 4 hours	C	Unknown
Ketamine	Unknown	1.26	Unknown	NA	No human data; unchanged in pregnant ewe
Midazolam	Not recommended during first trimester; may require dose increase for intended effect at term	0.15-0.66	0.15; cleared in 4 hours	D	Peak plasma concentration is reduced; half-life unchanged CYP3A-induced hepatic metabolism increased
Propofol	2 mg/kg resulted in less neonatal depression	0.7-1.3	Negligible	B	C ₅₀ for loss of consciousness unchanged first trimester
Thiopental	No dose change	0.4-1.1	<1	NA	Volume of distribution and clearance increased resulting in lower plasma concentrations but more efficacious in pregnancy

Abbreviations: FDA, U.S. Food and Drug Administration; F/M, fetal/maternal; NA, not applicable; PK/PD, pharmacokinetic/pharmacodynamic.

^aFrom Ansari J, Carvalho B, Shafer SL, Flood P. Pharmacokinetics and pharmacodynamics of drugs commonly used in pregnancy and parturition. *Anesth Analg*. 2016;122(3):786-804.
doi:10.1213/ANE.0000000000001143. Review, with permission.

TABLE 45.1E

Muscle relaxants^a

Drug	Dose adjustment	F/M ratio	Breast milk/maternal plasma ratio	Former FDA category	PK/PD alteration
Atracurium	Unchanged	0.12	Unknown; not orally absorbed by infant	C	VD, V _{ss} , and V _c unchanged; clinical duration unchanged
Pancuronium	Unchanged	0.2-0.5	Unknown; not orally absorbed by infant	C	Faster clearance no change in VD
Rocuronium	No change in initial dose; some studies suggest prolonged duration and therefore decreased redosing	0.1-0.6	Unknown; not orally absorbed by infant	C	PK unknown; onset unchanged; possible increased clinical duration of action
Succinylcholine	No change except avoid in women with atypical cholinesterase	Not detectable	Unknown; not orally absorbed by infant	C	Slightly prolonged recovery time postpartum Reduced cholinesterase not significant with 1 mg/kg dose, prolonged

					blockade may occur with larger doses
Vecuronium	May require more frequent monitoring	0.1-0.5	Unknown; not orally absorbed by infant	C	VD, Vss, and Vc unchanged; terminal half-life reduced but clinical duration is prolonged

Abbreviations: FDA, U.S. Food and Drug Administration; F/M, fetal/maternal; PK/PD, pharmacokinetic/pharmacodynamics; Vc, central volume; VD, volume of distribution; Vss, steady state volume.

^aFrom Ansari J, Carvalho B, Shafer SL, Flood P. Pharmacokinetics and pharmacodynamics of drugs commonly used in pregnancy and parturition. *Anesth Analg*. 2016;122(3):786-804.
doi:10.1213/ANE.0000000000001143. Review, with permission.

TABLE 45.1F

Local anesthetic drugs^a

Drug	Dose adjustment	F/M ratio	Breast milk/maternal plasma ratio	Former FDA category	PK/PD alteration
2-Chlorprocaine	N/A; titrated to effect	Rapidly hydrolyzed by esterases, and only traces of this compound reach the fetus, even after overdose, suggesting safety for the fetus	Unknown	C	Unknown
Bupivacaine	N/A; titrated to effect	0.3-0.7; 90% binding to maternal α_1 -acid glycoprotein that exceeds fetal protein binding (50%); fetal acidosis will cause increased fetal accumulation and possible toxicity.	0.3	C	No change in absorption or peak concentration; some changes in metabolism—less 4'-hydroxylation, enhanced N-dealkylation
Lidocaine	N/A; titrated to effect	0.5-0.9; acidosis increases transfer to fetus	1	B	Unknown
Mepivacaine	N/A; titrated to effect	0.5-0.7	Unknown	C	Unknown
Prilocaine	N/A; titrated to effect	1	Unknown	B	Unknown
Ropivacaine	N/A; titrated to effect	0.3-0.7	0.25	B	Unknown

Abbreviations: FDA, U.S. Food and Drug Administration; F/M, fetal/maternal ratio; N/A, not applicable; PK/PD, pharmacokinetic/pharmacodynamics.

^aFrom Ansari J, Carvalho B, Shafer SL, Flood P. Pharmacokinetics and pharmacodynamics of drugs commonly used in pregnancy and parturition. *Anesth Analg*. 2016;122(3):786-804.
doi:10.1213/ANE.0000000000001143. Review, with permission.

TABLE 45.1G

Antibiotic drug^a

Drug	Dose adjustment	F/M ratio	Breast milk/maternal plasma ratio	Former FDA category	PK/PD alteration
Amoxicillin	Higher more frequent dosing	0.18 after 3 minutes	0.014, 0.013, and 0.043 at 1, 2, and 3 hours	B	Increased clearance
Ampicillin	Higher more frequent dosing	0.3-0.7 at 1 hour after dose; 1.1-10 2-6 hours after dosing	0.2	B	Increased clearance in pregnancy
Azithromycin	500 mg before cesarean delivery leads to sustained concentrations greater than MIC for <i>Ureaplasma</i>	0.2-0.4	Accumulates reaches steady state in 3 days	B	Clearance by hepatobiliary excretion may be reduced in pregnancy.

Cefazolin	Higher dose to reliably keep plasma concentration above MIC	0.35-0.69	0.02	B	Clearance and volume of distribution are increased.
Cefepime	Higher dose or increased frequency may be required	0.23	Low concentration	B	Clearance and volume of distribution are increased.
Cefoxitin	Higher dose or increased frequency may be required; more studies needed	0.1-0.9	Minimal secretion	B	Clearance and volume of distribution are increased
Ceftriaxone	More studies needed	Unknown	0.03-0.06	B	? longer half-life in pregnancy
Ciprofloxacin	Unknown	Unmeasured but crosses placenta and concentrates in amniotic fluid	4.71	C	Unknown
Clindamycin	Increased dosing may be required depending on degree of protein binding; more research needed	0.5	0.08-3.1	B	Decreased AUC/MIC ratio
Ertapenem	Unknown	Low molecular weight; may pass	0.13-0.38	B	Unknown
Gentamicin	Increased frequency of dosing; may require measurement of plasma levels	0.34-0.44 were at 1-2 hours	0.1 at 1 hour and 0.4 at 7 hours	D	Increased volume of distribution and increased clearance result in low-peak concentrations.
Meropenem	Unknown	Unknown	0.18	B	Unknown
Metronidazole	No dose adjustment required	1	1	B	Unchanged
Moxifloxacin	Requires increased dosing	0.78	Unknown	C	Peak serum concentrations decreased; clearance increased; AUC 0.2 times nonpregnant values
Piperacillin and tazobactam	Increased frequency of dosing	0.17-0.27	Unknown	B	Increased clearance and volume of distribution; concentration less than MIC at 4 hours
Sulfonamides	Likely reduced concentration due to dilution but not described	0.5 sulfasalazine; 0.06 sulfisoxazole	Competes with bilirubin for albumin binding at birth	Sulfasalazine-B Sulfamethoxazole/trimethoprim-D Sulfamethoxazole-C	Unknown
Tetracyclines	Not tested; teratogenicity	Crosses and leads to dental discoloration	Crosses and leads to dental discoloration	D	Unknown
Vancomycin	20 mg/kg every 8 hours measurement of maternal plasma levels for sustained treatment	1 with steady state reached at 1-2 hours	1	C	Increased volume of distribution, and clearance, unknown changes in half-life

Abbreviations: AUC, area under the curve; FDA, U.S. Food and Drug Administration; F/M, fetal/maternal; MIC, minimum inhibitory concentration; PK/PD, pharmacokinetic/pharmacodynamics.

^aFrom Ansari J, Carvalho B, Shafer SL, Flood P. Pharmacokinetics and pharmacodynamics of drugs commonly used in pregnancy and parturition. *Anesth Analg*. 2016;122(3):786-804.
doi:10.1213/ANE.0000000000001143. Review, with permission.

As a general rule, molecular characteristics that favor the passage of drugs across the blood-brain barrier also allow for passage across the placenta. Knowledge of principles of placental transfer is important and can be utilized to achieve certain anesthetic goals. For example, during fetal surgery, drugs that cross the placenta

are used when possible to provide fetal anesthesia and analgesia. Drugs that do not cross the placenta such as muscle relaxants have to be directly administered to the fetus through the umbilical vein.

During cesarean section, limiting cardiac and respiratory depressant drugs that cross the placenta minimizes the risk of neonatal depression at birth. For example, whereas most benzodiazepines have a fetal to maternal (F/M) ratio of 1, midazolam is the exception with an F/M ratio that has been measured at 0.15 to 0.66, making it the preferred benzodiazepine when needed peripartum.⁸³ The ratio of breast milk to maternal plasma concentration is low at 1.2 and cleared by 4 hours. It is important to note that older recommendations restricting breastfeeding based on peripartum treatment with opioids, benzodiazepines and anesthetics have been revised in view of the importance of early initiation of breastfeeding success and overall health benefits from breastfeeding.⁸⁴ Many, but not all, drugs commonly used in pregnancy have available information on F/M ratio (see [Table 45.1A–G](#)) and breast milk to maternal plasma ratio.

Maternal Physiology

Physiologic Changes During Pregnancy and Delivery

During pregnancy and the peripartum period, substantial changes in maternal anatomy and physiology occur secondary to changes in hormone activity, increased maternal metabolic demands, biochemical alterations from the fetus, and the mechanical effects of an enlarging uterus ([Table 45.2](#)).

TABLE 45.2

Change in physiologic values in pregnancy

Factors	% Change from nonpregnant state
Central nervous system	
Minimal alveolar concentration for volatile anesthetics	-40
Cardiovascular system	
SVR	-15
HR	+15
SV	+30
BP	+35
CO	+40
PV	+45
Respiratory system	
FRC	-20
HCO ₃	-15
Paco ₂	-15
Pao ₂	+10
RR	+15
Oxygen consumption	+20
Tidal volume	+40
Minute ventilation	+50
Hematologic system	
Hemoglobin	-20
Clotting factors	+50-200
Renal system	
GFR	+50

Abbreviations: BP, blood plasma; CO, cardiac output; FRC, functional residual capacity; GFR, glomerular filtration rate; HCO₃, bicarbonate; HR, heart rate; PV, peripheral vasodilation; RR, respiratory rate; SV, stroke

volume; SVR, systemic vascular resistance.

Cardiovascular Changes

Pregnancy-induced changes in the maternal cardiovascular system include increased blood volume and cardiac output, decreased vascular resistance, and supine hypotension.

Intravascular Volumes and Hematology

Maternal intravascular fluid volume begins to increase in the first trimester of pregnancy as the result of increased production of renin, angiotensin, and aldosterone, which together promote sodium absorption and water retention. These changes are likely induced by progesterone.⁸⁵ With increases in plasma volume, there is an associated reduction in maternal plasma protein concentration. By term gestation, the plasma volume increases approximately 50%, and the red cell volume increases about 25%. The greater increase in plasma volume is the cause of the “physiologic anemia of pregnancy” (Figure 45.1).⁸⁶ Because the increase in red cell mass lags behind the increase in plasma volume, hematocrit typically reaches a nadir in the second trimester and increases by term. Maternal hemoglobin normally remains at 11 g/dL or greater even at term, and lower values at any time during pregnancy represent anemia. The physiologic anemia of pregnancy does not cause a reduction in oxygen delivery because of a coincident increase in cardiac output. The additional intravascular fluid volume (1,000–1,500 mL at term) compensates for an average 300 to 500 mL blood loss with vaginal delivery and 800 to 1,000 mL estimated blood loss with cesarean section. Following delivery, uterine contraction creates an autotransfusion of blood often in excess of 500 mL that also compensates for the acute blood loss from delivery. Mild thrombocytopenia is a normal finding.⁸⁷ However, 8% of otherwise healthy women have thrombocytopenia with a platelet count less than 150,000/ μ L. In the absence of other hematologic abnormalities, the cause for gestational thrombocytopenia is a diagnosis of exclusion. Platelet count does not usually drop below 70,000/ μ L and is not associated with abnormal bleeding. Gestational thrombocytopenia is thought to result from a combination of hemodilution and accelerated platelet turnover.

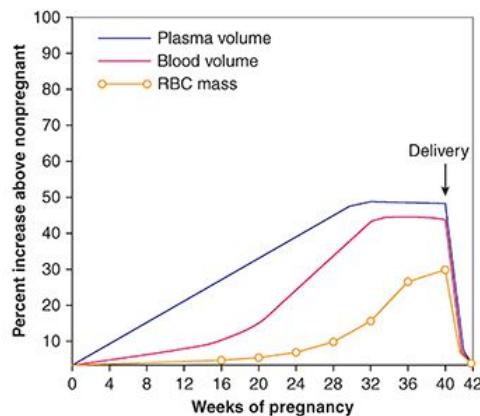


FIGURE 45.1 Blood volume changes during pregnancy. Plasma volume increases during pregnancy more rapidly than red cell mass leading to a physiologic anemia of pregnancy. Abbreviation: RBC, red blood cell.

Mild leukocytosis unrelated to infection is common during pregnancy.⁸⁸ In particular, the neutrophil count increases at term and is further increased during labor. These changes revert to normal during the week after delivery. In spite of mild thrombocytopenia, pregnancy is a hypercoagulable state with increased clotting and decrease in fibrinolytic capacity. Thrombogenic factors such as VII, VIII, and X, von Willebrand factor, and fibrinogen are increased,⁸⁷ whereas protein S and antithrombin III are decreased. These result in important changes to standard laboratory analyses depending on trimester (Table 45.3). Because pregnancy is associated with a near fivefold increased risk of venous thromboembolism, it is important to consider strategies that balance the maternal risk of thrombosis with hemorrhage while considering the potential fetal

risk from exposure to the anticoagulant agent. For example, warfarin is considered to provide the best protection against thromboembolic events; however, it crosses the placenta and therefore carries a dose-dependent risk of adverse fetal outcomes. Heparin preparations, on the other hand, do not cross the placenta and therefore do not exert direct effects on the fetus. When low molecular weight heparin is used, peak anti-Xa levels should be assessed and maintained between 1.0 and 1.2 U/mL. However, low-risk pregnant women who are on low molecular weight heparin for prevention likely do not need special monitoring. For patients on therapeutic anticoagulation, switching to intravenous unfractionated heparin is indicated in anticipation of planned delivery as its rapid onset and clearance minimizes potential complications from bleeding. Fondaparinux use is safe during pregnancy and recommended in the setting of heparin allergy or heparin-induced thrombocytopenia. Use of oral direct thrombin and factor Xa inhibitors during the pregnancy is limited as these agents cross the placenta.⁸⁹

TABLE 45.3

Standard hematology laboratory values during pregnancy^a

	First trimester	Second trimester	Third trimester
aPTT (seconds)	26.4-41.9	24.4-35.8	25.6-34.9
PT (seconds)	9.7-12.5	8.5-13.2	8.6-12.4
Fibrinogen (g/L)	2.38-4.44	2.40-5.97	2.79-5.91
D-dimer (μ g/mL)	0.01-0.31	0.05-0.73	0.14-2.82

Abbreviations: aPTT, activated partial thromboplastin time; PT, prothrombin time.

^aBased on 2.5th to 97.5th percentile reference intervals.

Obstetric hemorrhage has unique features in that there is a disproportional coagulopathy observed relative to total blood loss when compared with surgical or traumatic hemorrhage.⁹⁰ The rapid development of coagulopathy in obstetric hemorrhage is likely multifactorial and not completely understood, but the active consumption of procoagulant factors is thought to occur as the placenta separates from the uterus. Increased fibrinolysis and platelet activation are observed, as well as release of tissue factor into the blood stream, further activating consumption of procoagulant factors. Viscoelastic assays measure the hemostatic properties of whole blood by providing a real-time examination of the initiation, propagation, strength, and dissolution of clot. Thromboelastograph (TEG) and rotational thromboelastometry (ROTEM) are more representative of in vivo coagulation than standard laboratory tests and are increasingly being used in the management of obstetric hemorrhage and hemostatic disorders. Interestingly, a strong correlation has been identified between ROTEM variables and standard coagulation parameters in healthy women soon after delivery.⁹¹ Meanwhile, use of TEG has demonstrated increased coagulability in preeclamptic patients that was not revealed in standard laboratory tests.⁹² The correlation between TEG and standard laboratory values has been inconsistently described in the literature. Issues such as fibrinogen overestimation⁹³ have also been reported with the use of TEG. The FIBTEM component of the ROTEM assay evaluates fibrinogen and appears to correlate well with standard laboratory fibrinogen levels. Thus, ROTEM analyses may be better suited for perioperative guidance in fibrinogen administration. Until there is a direct comparison between TEG and ROTEM in the obstetric population, it remains unclear which is superior for the diagnosis and goal-directed management of coagulopathy during obstetric hemorrhage.

Cardiac Output

By the end of the first trimester, maternal cardiac output increases, on average, by 35% above prepregnancy values and continues to increase to 50% above nonpregnant values by the end of the second trimester, remaining at similar, elevated levels throughout the third trimester. This increased cardiac output is the result of both increases in stroke volume and heart rate (Figure 45.2).⁹⁴ Labor is associated with further increases in cardiac output, which increases with each uterine contraction. Increases above prelabor values of 10% to 25% are noted during the first stage of labor and a 40% increase occurs during the second stage. The largest increase in cardiac output occurs immediately after delivery, when cardiac output can be increased by 80% to

100% above prelabor values. This large increase is secondary to the autotransfusion from the final uterine contraction, reduced vascular capacitance from loss of the placenta, and decreased lower extremity venous pressure from release of the aortocaval compression. This massive increase in cardiac output represents a moment of unique risk for patients with cardiopulmonary disease, particularly those with valvular stenosis and pulmonary hypertension. Cardiac output returns toward prelabor values by about 24 hours postpartum and returns to nonpregnant levels within 12 weeks after delivery. It is critical to monitor patients with cardiac disease closely in the postpartum period.

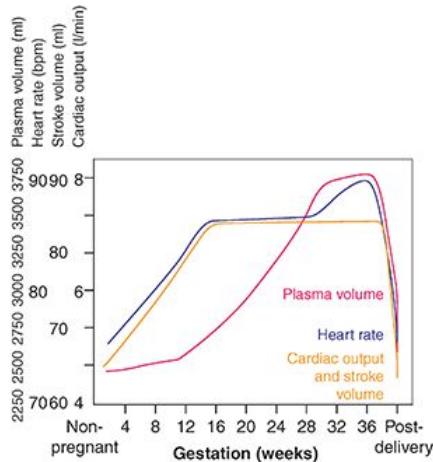


FIGURE 45.2 Maternal hemodynamic changes of pregnancy. Maternal heart rate and cardiac output increase early in the first trimester and plateau in the second trimester. There is an additional increase in heart rate during the third trimester. Plasma volume increases throughout the first and second trimester and reaches a plateau during the third trimester. All values drop rapidly in the days after delivery. *Reproduced from Thorne SA. Pregnancy in heart disease. Heart. 2004;90(4):450-456 with permission from BMJ Publishing Group Ltd.*

Systemic Vascular Resistance

In spite of increases in cardiac output and plasma volume, systemic blood pressure normally decreases secondary to a 20% reduction in systemic vascular resistance by term. Blood pressure decreases approximately 20% by 20 weeks' gestational age and then increases toward nonpregnant values as the pregnancy reaches term. Central venous pressure and pulmonary capillary wedge pressure are unchanged during normal pregnancy despite the increase in plasma volume because of the concurrent increase in venous capacitance.

Aortocaval Compression

In the supine position, blood pressure commonly decreases as the result of aortocaval compression by the gravid uterus. At term, there is often nearly complete occlusion of the inferior vena cava in the supine position, with return of blood from the lower extremities through the epidural, azygos, and vertebral veins. Despite the increase in collateral venous return to the heart, magnetic resonance imaging in healthy late term pregnancy shows a 16% reduction in cardiac output associated with the supine position.⁹⁵ Aortocaval compression can manifest in symptoms of diaphoresis, nausea, vomiting, and dizziness and may exacerbate lower extremity venous stasis, thereby resulting in ankle edema, varices, and increased risk of venous thromboembolism.

Compensatory mechanisms to mitigate supine hypotension from aortocaval compression include an increase in sympathetic nervous system activity to increase systemic vascular resistance and maintain systemic blood pressure despite a reduced cardiac output. Because neuraxial or general anesthesia may impair this compensatory sympathetic response, traditional clinical practice during surgical delivery has been to

place the patient in 15 degree left lateral tilt to displace the gravid uterus away from the inferior vena cava. For the healthy parturient, debate exists regarding the practicality and the continued need in contemporary clinical practice, when maternal blood pressure is maintained by expanding intravascular volume afterload is assured with prophylactic phenylephrine infusion during cesarean delivery.⁹⁶ These considerations do not apply to emergency situations with unstable mothers or fetuses. As of its latest update, the American Heart Association continues to recommend placing the unstable pregnant patient in full left lateral decubitus position while investigating and treating precipitating factors (class I; level of evidence C). However, in the event of maternal cardiac arrest, chest compressions should be delivered with the patient in the supine position with a firm backboard while a separate provider performs continuous manual left uterine displacement.⁹⁷

It is important for the anesthesiologist to recognize changes to the normal cardiac exam as a result of aforementioned cardiovascular changes of pregnancy. Auscultation may reveal an accentuated first heart sound (S_1) with an increased splitting of the first heart sound caused by dissociated closure of the tricuspid and mitral valves. A third heart sound (S_3) is often heard in the final trimester and a fourth heart sound (S_4) can also be heard in a minority of pregnant patients as a result of increased volume and turbulent flow. A mild systolic ejection (grade 2/6) murmur is commonly noted over the left sternal border and is secondary to mild regurgitation at the tricuspid valve from increased cardiac volume.

Pulmonary Changes

Pregnancy results in significant alterations in the upper airway, lung volumes, minute ventilation, oxygen consumption, and metabolic rate.

Airway

The occurrence of difficult and failed tracheal intubation are both more common in the pregnant patient (**Table 45.4**). During pregnancy, there is vascular engorgement of the mucosal lining of the oro- and nasopharynx, which can result in bleeding with instrumentation of the airway. Therefore, attempts at laryngoscopy should be minimized and a smaller size cuffed endotracheal tube (6.0- to 6.5-mm internal diameter) should be considered. Labor considerations can worsen the maternal airway—bearing down and Valsalva maneuver can increase hydrostatic venous pressure; oxytocin administration, which contains antidiuretic properties, can increase hydrostatic venous pressure thereby further worsening airway tissue edema. It is important to note that both normotensive and preeclamptic patients are susceptible to increases in soft tissue thickness at the level of the hyoid bone as well as the progression to a higher Mallampati grading score following labor and delivery.⁹⁸ In addition, pregnancy-associated weight gain, particularly in women of short stature or with preexisting obesity, can exacerbate difficult laryngoscopy because of a shorter neck and heavy breast tissue.

TABLE 45.4

Effect of pregnancy on intubation^a

	Nonpregnant population	Pregnant population
Incidence of difficult intubation	1:50	1:21
Incidence of failed intubation	1:2,230	1:280

^aFrom McKeen DM, George RB, O'Connell CM, et al. Difficult and failed intubation: incident rates and maternal, obstetrical, and anesthetic predictors. *Can J Anaesth*. 2011;58:514-524; Yentis SM. Predicting difficult intubation—worthwhile exercise or pointless ritual? *Anaesthesia*. 2002;57(2):105-109; Kinsella SM, Winton AL, Mushambi MC, et al. Failed tracheal intubation during obstetric general anaesthesia: a literature review. *Int J Obstet Anesth*. 2015;24(4):356-374; King TA, Adams AP. Failed tracheal intubation. *Br J Anaesth*. 1990; and Samsoon GL, Young JR. Difficult tracheal intubation: a retrospective study. *Anaesthesia*. 1987;42(5):487-490.

Video laryngoscopy has become routine use to prevent or rescue a difficult intubation. Changes in the pregnant woman's airway can make laryngeal mask airway (LMA) insertion and front-of-neck airway access (FONA) particularly challenging. Guidelines have incorporated the immediate use of a second-generation supraglottic airway after failed intubation as an alternative to facemask ventilation in the pregnant patient. A critical concern in the parturient is the risk of regurgitation and aspiration due to increased intragastric pressure and decreased lower esophageal sphincter tone. However, the use of an LMA as a rescue airway in the carefully selected low-risk obstetric patient has several advantages—large-scale studies have demonstrated high rates of successful first insertion attempts as well as rapid time to establish ventilation without clinical evidence of gastric regurgitation or aspiration.^{99–101} If an LMA is to be used, it is recommended that it contain a double lumen with separate respiratory and gastrointestinal tract to allow suctioning of gastric contents.

The severely obese parturient poses an increased risk of failed intubation during general anesthesia for cesarean section that may deteriorate to a “cannot intubate, cannot oxygenate” scenario. Because FONA would be the definitive life-saving management in this situation, there has increased attention on the utility of certain ultrasound-based measurements to expedite the location of the cricothyroid membrane. A brief preprocedural ultrasound of the anterior infraglottis to identify a bright hyperechoic line indicating the cricothyroid membrane air-tissue border may aid in the airway management of severely obese parturients. Should the scenario of failed intubation arise and FONA is required, preobtained knowledge of the cricothyroid membrane depth would help the clinician more accurately access the airway lumen, lessen the risk of airway trauma, and minimize the risk of hypoxic injuries ([Figure 45.3](#)).¹⁰² While preprocedural ultrasound examination of the infraglottic airway may not always be feasible, all necessary equipment for difficult airway management should be immediately available and the patient's position fully optimized before proceeding with intubation.

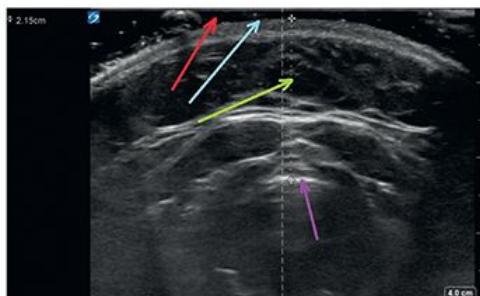


FIGURE 45.3 Transverse ultrasound scan for cricothyroid membrane identification in a patient with BMI $>45 \text{ kg/m}^2$. Red arrow refers to ultrasound gel (between transducer and skin); blue arrow refers to skin; green arrow refers to cricothyroid membrane (CTM) depth (21.5 mm as indicated by caliper measurements); purple arrow refers to air-tissue border of the CTM. *Reprinted from Gadd K, Wills K, Harle R, et al. Relationship between severe obesity and depth to the cricothyroid membrane in third-trimester non-labouring parturients: a prospective observational study. Br J Anaesth. 2018;120(5):1033–1039. Copyright © 2018 British Journal of Anaesthesia.*

Minute Ventilation and Oxygenation

In order to accommodate the increased oxygen demand and carbon dioxide production of the growing placenta and fetus, minute ventilation is increased 45% to 50% above nonpregnant values during the first trimester and remains at this increased level for the remainder of the pregnancy. This greater minute ventilation is attained primarily as a result of a greater tidal volume with a small increase in the respiratory rate ([Figure 45.4](#)).¹⁰³ Maternal PaCO_2 is commonly reduced from 40 mm Hg to approximately 30 mm Hg during the first trimester. Arterial pH, however, is only slightly increased (pH 7.42–7.44) because of metabolic compensation from increased renal excretion of bicarbonate (HCO_3^- is typically 20 or 21 mEq/L at term).

During the first trimester, maternal PaO_2 may be above 100 mm Hg due to hyperventilation and decreased alveolar CO_2 . Later, PaO_2 becomes normal or even slightly decreased, most likely reflecting small airway closure with normal tidal volume ventilation and intrapulmonary shunt. Arterial oxygenation can be significantly improved by changing position from supine to lateral. Maternal hemoglobin is right shifted with the P_{50} increasing from 27 to approximately 30 mm Hg.¹⁰⁴ The higher P_{50} in the mother and lower P_{50} in the fetus favors off-loading of oxygen across the placenta. At term, oxygen consumption is increased by 20%. During the first stage of labor, oxygen consumption increases above prelabor values by 40% and during the second stage, it is increased by 75%. In the absence of analgesia, the pain of labor can result in severe hyperventilation causing PaCO_2 to decrease below 20 mm Hg.

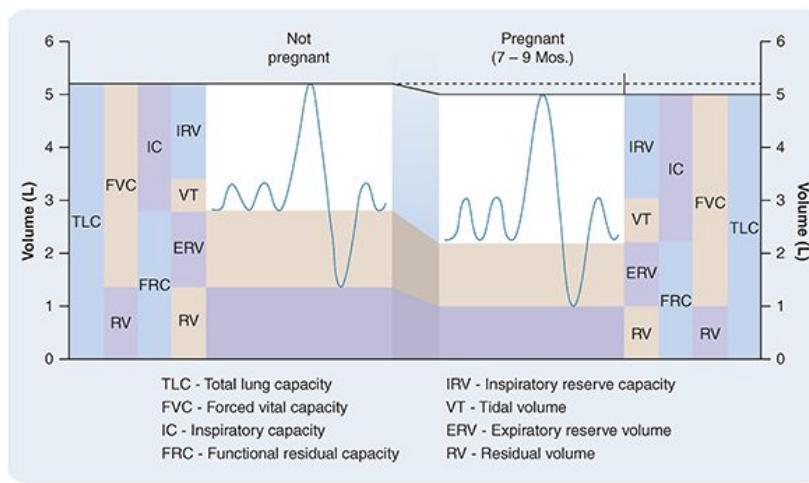


FIGURE 45.4 Changes in maternal pulmonary function. Functional residual capacity is reduced by virtue of reductions in expiratory reserve volume and residual volume during pregnancy. Inspiratory capacity is increased resulting from an increase in tidal volume. *Reprinted from Hegewald MJ, Crapo RO. Respiratory physiology in pregnancy. Clin Chest Med. 2011;32(1):1-13. Copyright © 2011 Elsevier. With permission.*

Lung Volumes

During pregnancy, the growing uterus elevates the diaphragm and causes a reduction in functional residual capacity by 20% at term. This reduction in functional residual capacity is a result of equal reduction in both the expiratory reserve volume and residual volume (see [Figure 45.4](#)). The closing capacity remains unchanged. The reduced ratio of functional residual capacity to closing capacity favors small airway closure with reduced lung volumes and in the supine position causing atelectasis. Vital capacity is not significantly changed with pregnancy. The combination of increased minute ventilation and decreased functional residual capacity results in a greater rate at which changes in the alveolar concentration of inhaled anesthetics can be achieved with spontaneous ventilation in the case of mask induction.

During induction of general anesthesia in a pregnant patient, desaturation occurs more rapidly than in a nonpregnant patient because of decreased functional residual capacity and increased metabolic rate. Administration of 100% oxygen prior to the induction of general anesthesia is critical to allow as much time as possible for safe airway management. Inhalation of 100% oxygen for 3 minutes or, in an emergency, 4 maximal breaths over the 30 seconds will significantly prolong the period between apnea and arterial oxygen desaturation.

A novel technique for oxygenating the pregnant patient during induction of general anesthesia is with transnasal humidified rapid-insufflation ventilatory exchange—an open-airway technique that refers to the use of warmed and humidified high-flow nasal oxygen (70-90 L per minute) in an apneic patient. There are several advantages to this strategy—the high flow generates turbulence, thereby facilitating gas exchange and generating continuous positive pressure to reduce the likelihood of atelectasis and collapse of soft airway

tissue. Because transnasal humidified rapid-insufflation ventilatory exchange can be continued during efforts to secure an airway, it should be considered for any patient identified as a potential difficult airway. However, judicious use in certain pregnant patients is warranted as there are risks of an unprotected airway as well as maternal accumulation of carbon dioxide, albeit at a slower rate than with classic apneic oxygenation. While the use of high-flow nasal oxygen to optimize preoxygenation of the pregnant patient prior to induction of general anesthesia is currently supported by guidelines,¹⁰⁵ further investigation is needed to determine the precise rate of maternal carbon dioxide level accumulation and quantification of fetal acidosis risk.

Gastrointestinal Changes

After midgestation, pregnant women are thought to be at increased risk of aspiration pneumonia with administration of general anesthesia. This increased risk is caused by several factors. There is upward movement of the esophageal sphincter by the gravid uterus. Increased progesterone and estrogen concentrations during pregnancy also contribute to reduced esophageal sphincter tone. Gastrin is secreted by the placenta, which increases gastric acid secretion. Together, these changes result in an increased incidence of gastroesophageal reflux during pregnancy. Gastric emptying is not changed during pregnancy before the onset of labor in women who are of normal weight or obese.^{106,107} However, during labor, pain, anxiety, and the administration of opioids (including those administered neuraxially) decrease gastric emptying. An increase in the residual volume of gastric content can further increase the risk of aspiration, which is already elevated during pregnancy.¹⁰⁸ As a result, all women in labor are considered to have “full stomachs” and to be at increased risk for pulmonary aspiration with induction of anesthesia. In studies comparing a nonparticulate antacid in addition to an H₂ antagonist, the H₂ antagonist is superior to achieve an intragastric pH of greater than 2.5 at intubation compared to placebo or antacid alone.¹⁰⁹

It was traditionally recommended that women past midgestation receive general anesthesia with rapid sequence induction, cricoid pressure, and placement of a cuffed endotracheal tube rather than monitored anesthesia care or an LMA for aforementioned reasons. However, the incidence of pulmonary aspiration during deep sedation for second-trimester dilation and evacuation in an outpatient pregnant population between 14 and 24 weeks’ gestation was found to be 0.04% to 0.08%.^{110,111} Thus, although there remains a theoretical risk of aspiration, the true incidence appears small. As always, the risks and benefits of tracheal intubation must be weighed in this midgestation population.

Although blood flow to the liver does not change beyond that related to the increased cardiac output during pregnancy, markers of liver function including aspartate aminotransferase, alanine aminotransferase, and bilirubin all increase to the upper limits of normal. Alkaline phosphatase levels more than double as a result of the placental production of this enzyme. Hemodilution during pregnancy is responsible for lower plasma protein concentrations. Lower serum albumin concentrations can result in elevated free blood levels of highly protein-bound drugs. Plasma cholinesterase (pseudocholinesterase) activity is decreased about 30% from the 10th week of gestation up to 6 weeks postpartum, but this decreased cholinesterase activity is not associated with clinically relevant prolongation of neuromuscular blockade from succinylcholine or mivacurium in patients with normal baseline levels of the enzyme. Gallbladder disease is common during pregnancy due to incomplete gallbladder emptying and changes in bile composition.

The use of bedside ultrasonography of the gastric antrum in nonpregnant adults has been well described and may serve as a vital tool in the preoperative assessment of the pregnant patient. Pregnancy presents unique challenges to this exam given the cephalad displacement of the stomach by the gravid uterus as well as difficulty in probe placement between the xiphoid process and abdomen. Mathematical models using magnetic resonance imaging measurements of the gastric antrum in pregnancy are currently being developed to allow for correlation of antrum area to content volume. This is currently an active area of research with many variables at play given that gastric emptying is delayed during labor, institutions vary based on fasting policy, and different intravenous and regional opioids may be utilized. The gastric ultrasound examination may one day prove useful in identifying the “full stomach” patient, thereby allowing the anesthesiologist to identify those at greatest risk for pulmonary aspiration should general anesthesia be required.

Renal Changes

Renal blood flow and glomerular filtration rate are increased 50% by the second trimester and remain elevated until 3 months postpartum ([Figure 45.5](#)). As a result, clearance of creatinine, urea, and uric acid are increased during pregnancy. Increased urine protein and glucose concentrations result from decreased renal tubular resorption capacity. The upper limit of the normal 24-hour urine elimination during pregnancy is 300 mg of protein and 10 g glucose. Medications that are renally excreted may require preemptive dose escalation throughout pregnancy.

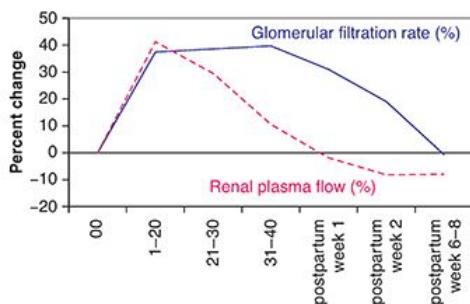


FIGURE 45.5 Percentage change from baseline glomerular filtration rate and renal plasma flow throughout each trimester of pregnancy and initial postpartum period. *Reprinted from Cheung KL, Lafayette RA. Renal physiology of pregnancy. Adv Chronic Kidney Dis. 2013;20(3):209-214. Copyright © 2013 National Kidney Foundation, Inc. With permission.*

Neurologic Changes

Pregnant patients are more sensitive to both inhaled and local anesthetic agents. The minimum alveolar concentration (MAC) is reduced by 30% by the first trimester of pregnancy. The MAC or immobility in response to volatile anesthetics occurs at the level of the spinal cord. A study using electroencephalography suggested that anesthetic effects of sevoflurane on the brain are similar in the pregnant and nonpregnant state.¹¹² Fortunately, anesthetic concentrations required for hypnosis and amnesia are approximately half of MAC or the concentration required to prevent activation of spinal reflexes. Unanticipated awareness is more common during cesarean section. The reasons are likely multifactorial. There is often a desire to prevent anesthetic exposure to an already depressed fetus and the requirement for rapid surgery to allow for neonatal resuscitation may not allow the anesthetic to come to steady state before surgery begins. Even if not used subsequently, the muscle relaxant used to facilitate intubation will likely be in effect during delivery when the anesthetic concentration is increasing.

Pregnant women are more sensitive to the local anesthetics. A lower dose can provide the same level of either spinal or epidural neuraxial blockade compared to nonpregnant women. At term, distention of epidural veins decreases the size of the epidural space, and volume of cerebrospinal fluid in the subarachnoid space. Cerebrospinal fluid pressure is not increased during pregnancy until labor, when it is increased both during uterine contractions and expulsion of the fetus. Although the decreased volume of these spaces may facilitate spread of local anesthetics, the decreased local anesthetic required during pregnancy occurs as early as the first trimester, before mechanical or pressure related changes occur. As such, pharmacodynamic changes are likely more important in causing increased nerve sensitivity to local anesthetics (see “[Postoperative Pain Management](#)” section).

Uteroplacental Physiology

The placenta is composed of both maternal and fetal tissues and is the interface of maternal and fetal circulation systems. It provides a substrate for physiologic exchange between mother and fetus without immunologic rejection. Maternal blood is delivered to the placenta by the uterine arteries and enters the intervillous space via the spiral arteries. The deoxygenated fetal blood arrives at the placenta via two umbilical arteries that form umbilical capillaries that cross the chorionic villi. Following placental exchange,

oxygenated, nutrient-rich, and waste-free blood is returned from the placenta to the fetus through a single umbilical vein ([Figure 45.6](#)).

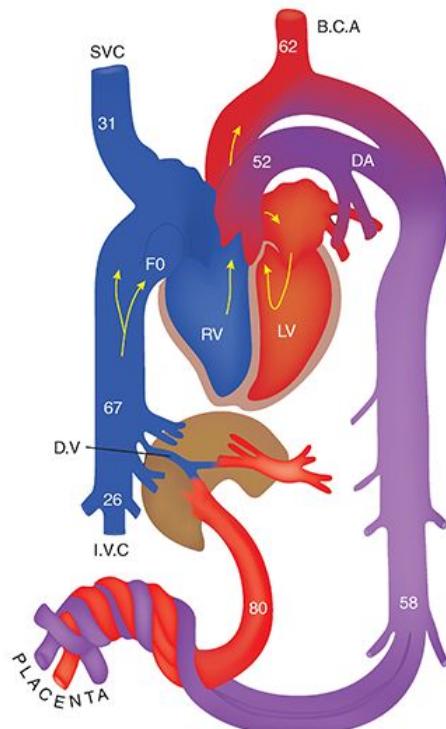


FIGURE 45.6 Diagram of the fetal circulation. Oxygenated blood flows in through the umbilical vein. It passes through the ductus venosus (DV) where it is diluted by deoxygenated blood returning from the inferior vena cava (IVC). Oxygenated blood passes to the right atrium, where little passes through the fetal lungs because of high pulmonary vascular resistance. Part of the circulation passes through the foramen ovale (FO) directly to the left atrium to enter the fetal systemic circulation. Another portion bypasses the lungs by passing from the pulmonary artery through the ductus arteriosus (DA) where it proceeds directly to the aorta. The numbers represent oxygen saturation at various points in the fetal circulation. Abbreviations: BCA, brachial cephalic artery; LV, left ventricle; RV, right ventricle; SVC, superior vena cava. *Reprinted with permission from Born GV, Dawes GS, Mott JC, et al. Changes in the heart and lungs at birth. Cold Spring Harb Symp Quant Biol. 1954;19:102-108. Copyright © 1954 by Cold Spring Harbor Laboratory Press.*

Uterine Blood Flow

An understanding of uteroplacental blood flow is important for the anesthesiologist caring for a pregnant patient. Uterine blood flow increases progressively during pregnancy from about 100 mL per minute in the nonpregnant state to 700 mL per minute (about 10% of cardiac output) at term gestation. Uterine blood flow has minimal autoregulation and the vasculature remains essentially fully dilated during normal pregnancy. Uterine and placental blood flows are dependent on maternal cardiac output and are directly related to uterine perfusion pressure. Decreased perfusion pressure can result from maternal hypotension secondary to hypovolemia, aortocaval compression, or decreased systemic resistance from either general or neuraxial anesthesia. Increased uterine venous pressure can also decrease uterine perfusion. This can occur from supine positioning with vena caval compression as discussed previously, frequent or prolonged uterine contractions, or significant prolonged abdominal musculature contraction (Valsalva) during pushing. Additionally, extreme hypocapnia ($\text{Paco}_2 < 20 \text{ mm Hg}$) associated with hyperventilation secondary to labor pain can reduce uterine blood flow with resultant fetal hypoxemia and acidosis. Neuraxial blockade does not alter uterine blood flow in the absence of maternal hypotension.

Endogenous maternal catecholamines and exogenous vasopressors may cause an increase in uterine arterial resistance and a decrease in uterine blood flow, depending on the type and dose given. In early studies in pregnant ewes, ephedrine was found to have no effect on uterine blood flow despite drug-induced increases in maternal arterial blood pressure, whereas other vasopressors including phenylephrine resulted in vasoconstriction and fetal acidosis.^{113,114} From this animal data, ephedrine was long considered the vasopressor of choice for the treatment of hypotension caused by the administration of neuraxial anesthesia to pregnant women. In complete contrast, however, clinical trials demonstrate the use of phenylephrine is not only effective in preventing hypotension but also is associated with less fetal acidosis and base deficit than the use of ephedrine.^{115,116} Thus, many clinicians have now switched from ephedrine to phenylephrine as the vasopressor of first choice for treating hypotension during labor and delivery. More recently, trials have investigated the utility of norepinephrine infusion to prevent maternal hypotension. A recent systemic review and meta-analysis reported on three randomized controlled trials that compared norepinephrine and phenylephrine between 2015 and 2018.¹¹⁷ The authors found that the two vasopressors were equally effective in treating maternal hypotension and both were considered safe with regard to neonatal outcomes based on umbilical vein blood gases and Apgar scores. Norepinephrine use was associated with less bradycardia and improved nausea and vomiting rates. Although it may serve as a promising alternative to phenylephrine, more studies are needed before changes to routine clinical practice can be recommended. Until then, the prudent use of norepinephrine should include consideration of tissue necrosis risk due to extravasation and avoidance in patients with known or suspected coronary artery disease.

Oxygen Transfer

The delivery of oxygen from the mother to the fetus is dependent on a variety of factors including placental blood flow, the oxygen partial pressure gradient between the two circulations, the diffusion capacity of the placenta, the respective maternal and fetal hemoglobin concentrations and oxygen affinities, and the acid-base status of the fetal and maternal blood (Bohr effect). The fetal oxyhemoglobin dissociation curve is left-shifted ($P_{50} = 19$ mm Hg, greater oxygen affinity), whereas the maternal oxyhemoglobin dissociation curve is right-shifted ($P_{50} = 27$ mm Hg, less oxygen affinity). This occurs because fetal hemoglobin does not interact with 2,3-disphosphoglycerate, facilitating oxygen transfer to the fetus (Figure 45.7). Fetal PaO_2 is normally 40 mm Hg and does not exceed 60 mm Hg even if the mother is breathing 100% oxygen. This is because significant oxygen has been extracted by the mother's tissues prior to arrival at the fetoplacental unit. Carbon dioxide easily crosses the placenta and is limited by blood flow and not diffusion.

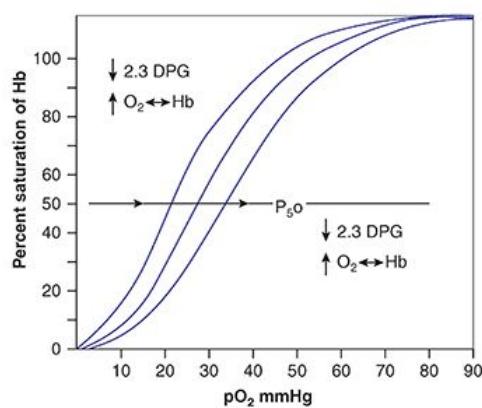


FIGURE 45.7 Right shift of maternal hemoglobin oxygen dissociation curve. Increased interaction with 2,3-disphosphoglycerate (2,3-DPG) results in hemoglobin with lower oxygen affinity and a right shift in the hemoglobin oxygen saturation curve. As a result, oxygen is more easily off-loaded to fetal hemoglobin, which has a left shifted hemoglobin oxygen dissociation curve. Reprinted with permission from Jepson JH. Factors influencing oxygenation in mother and fetus. *Obstet Gynecol*. 1974;44(6):906-914. Copyright © 1974 The American College of Obstetricians and Gynecologists.

Principles of Nonobstetric Surgery During Pregnancy

Fetal Heart Rate Monitoring

The most frequently used fetal electronic monitoring is based on Doppler ultrasound technology, relying on fetal cardiac activity itself or arterial flow through a major fetal vessel. After 18 weeks, fetal heart rate monitoring is practical, and after 25 weeks, variability in fetal heart rate is a reliable sign of well-being. The American College of Obstetrics and Gynecology states, “Although there are no data to support specific recommendations regarding non-obstetric surgery and anesthesia in pregnancy, it is important for non-obstetric physicians to obtain obstetric consultation before performing non-obstetric surgery. The decision to use fetal monitoring should be individualized and each case warrants a team approach for optimal safety of the woman and her baby.”¹¹⁸ Anesthetic agents reduce both baseline fetal heart rate and heart rate variability, so readings must be interpreted in context; general anesthesia, opioid use, and lower maternal body temperature may alter autonomic tone leading to an absence of fetal heart variability that is not necessarily indicative of fetal acidemia. Fetal bradycardia, of more concern, can also be affected by factors such as hypothermia, maternal acidosis, or the maternal administration of drugs that cross the placenta. Thus, knowledge of placental transfer of drugs that may affect fetal heart rate (such as β-blockers or acetylcholinesterase inhibitors) is paramount.

The theoretical benefit of intraoperative fetal heart rate monitoring is to detect early compromise, thereby allowing prompt optimization of maternal hemodynamics and oxygenation. Should fetal decelerations be observed, the surgeon should be notified and the obstetric team consulted. Monitoring of uterine activity is also important as variable decelerations caused by contractions or increased uterine irritability can alert whether surgical intraabdominal manipulation should be ceased or if tocolytic therapy is needed. Maternal hemodynamics should be addressed while in consultation with the obstetrician on the appropriateness of suppression therapy such as a magnesium infusion or bolus doses of IV nitroglycerin (100 µg) or terbutaline (0.25 mg).

Intraoperative Considerations for Nonobstetric Surgery

No single anesthetic approach has demonstrated a clear detriment to the fetus. Regardless of whether general, neuraxial, or regional anesthesia is administered, the principles of anesthetic management should be the following: Maintain the pregnant state, preserve maternal physiology with minimal perturbation, and ensure maternal oxygenation and uteroplacental perfusion by avoiding hypovolemia, hyperventilation, severe anemia, hypoxia, hypothermia, and uterine hypertonus. The choice of anesthesia should be guided by maternal indications as well as the site and nature of surgery.

If possible, a regional anesthesia may help allay concerns about teratogenicity in the first trimester. A reliable peripheral or neuraxial nerve block would limit unnecessary drug exposure to the fetus (assuming heavy sedation is avoided) and has the advantage of not interfering with fetal heart rate variability as much as general anesthesia. Furthermore, airway control is maintained and avoids the potential risk of prolonged or failed intubation, hypoxia, or aspiration, particularly in full stomach patients. However, pregnancy does lower the threshold for local anesthetic toxicity, so a dose reduction should be considered (about 30%).

Management of neuraxial anesthesia for nonobstetric surgery in the pregnant patient would be the same for cesarean delivery where the major concern is maternal hypotension and aggressive prevention and treatment of hypotension is critical. Volatile agents cause uterine relaxation, which may help prevent preterm contractions but induces undesirable hypotension in escalating doses. Because autoregulation is absent for the uteroplacental circulation, any reduction in maternal cardiac output or blood pressure may compromise placental perfusion and lead to fetal ischemia. Regardless of technique, focus should be on optimization of hemodynamics by maintaining uterine displacement (if the patient is beyond 20-24 weeks' gestational age), vasopressor therapy (selection of ephedrine or phenylephrine to be determined by maternal heart rate), and judicious resuscitation with either crystalloid or colloid.

Hemostatic resuscitation is vital to the stabilization of the pregnant trauma patient or during an obstetric hemorrhage. In the event of ongoing bleeding and resuscitation, the development of a dilutional coagulopathy is likely. Treatment with fibrinogen concentrate is most effective in patients with severe hypofibrinogenemia (see [Table 45.3](#)) and can help reduce the risk of overtransfusion and development of pulmonary edema.¹¹⁹ Although pregnant patients are at an elevated baseline risk for thromboembolism, this should not deter the clinician from considering antifibrinolytic therapy in the setting of hemorrhage. The landmark WOMAN (World Maternal Antifibrinolytic Trial) trial showed a survival benefit in postpartum hemorrhage when tranexamic acid was administered within 1 to 3 hours after delivery without increasing the rate of thromboembolic complication.¹²⁰ Hemorrhage from threatened abortions during the second or third trimester may benefit from tranexamic acid by arresting bleeding and prolonging pregnancy.¹²¹ Current clinical trials are underway to determine whether the use of tranexamic acid therapy is superior to expectant management for bleeding of unknown etiology during the second trimester.¹²²

Safety concerns exist surrounding blood product administration during pregnancy and the postpartum period given exposure of the mother to risks of alloimmunization and hemolytic disease of the fetus. Transfusion is rarely required in hemodynamically stable pregnant patient with hemoglobin >7.0 g/dL and should be reserved only in the event of active bleeding, major hemorrhage, or immediate need to correct cardiac decompensation. All products should be leukocyte depleted, and red blood cells should be tested for cytomegalovirus to reduce the risk of serious infection to the fetus.

Postoperative Pain Management

Maternal pain control after nonobstetric surgery is of paramount importance to maternal and fetal well-being as pain has been shown to increase the risk of premature labor. Although all opioids may be used in pregnancy, they do readily cross the placenta and may reduce fetal heart rate variability (although there is no evidence, this is detrimental to the fetus, and neonatal outcomes are usually reassuring). Repeated opioid exposure during third trimester should alert the neonatologist to monitor for neonatal abstinence syndrome. If the fetus is born shortly after exposure to maternal systemic opioids, reversal with naloxone and/or respiratory support may be necessary.

Regional nerve or plexus blockade can provide excellent postoperative analgesia and reduce the need for systemic opioids. Single-injection blocks have been performed in pregnant patients without significant complication to either mother or fetus.¹²³ In current practice, the long-acting local anesthetics ropivacaine and bupivacaine are most frequently used. The half-life of bupivacaine in the nonpregnant adult is 3.5 hours but can exceed 9 hours in the parturient.¹²⁴ α_1 Acid glycoprotein, a plasma protein that is significantly reduced in pregnancy, has a high binding affinity for local anesthetics and serves as a primary buffer to prevent local anesthetic toxicity. Because there is a decreased safety margin of local anesthetic infusions during pregnancy and an increase in susceptibility to local anesthetic systemic toxicity exists, the practice of catheter-based chronic local anesthetic infusion following peripheral nerve block during pregnancy is not supported.

Effective postoperative analgesia can also be provided by administering a long-acting narcotic neuraxially, such as preservative-free morphine, or by continuation of a combined opioid and local anesthetic epidural infusion. The addition of opioid permits reduction in the dose of local anesthetic needed. Thus, the low volume of local anesthetic and low dose of opioid drug associated with effective neuraxial dosing rarely poses a problem. Nonsteroidal anti-inflammatory drugs, although useful adjuvant analgesics outside of pregnancy, should be used with caution in pregnancy. They are associated with an increased risk of miscarriage and fetal malformation when used in early pregnancy and premature closure of the ductus arteriosus, reduced fetal renal reduction, and oligohydramnios when used after 32 weeks' gestation. Acetaminophen is an excellent opioid adjuvant and is the analgesic of choice for treatment of mild to moderate pain during any state of pregnancy.

Postoperative pain medications may make it difficult for the patient to note early contractions and patient perception should not be considered a substitute for standard monitoring. Thus, following surgery, both the fetal heart rate and uterine activity should be evaluated. In addition, venous thrombosis prophylaxis should be

instituted unless surgically contraindicated or until the patient can mobilize. Continued observation is important because the risk for adverse delivery outcome is elevated in women who have had nonobstetric surgery (after adjusting for age and other comorbidities).¹²⁵

Fetal Physiology

Characteristics of the Fetal Circulation

Approximately two-third of the fetal-placental blood volume is contained within the placenta. The fetal blood volume increases throughout gestation. During the second and third trimester, the fetal blood volume has been estimated to be approximately 120 to 160 mL/kg of fetal body weight.

The fetal blood passes from the placenta through the umbilical vein (see [Figure 45.6](#)).¹²⁶ Approximately one-third of the blood volume passes through the ductus venosus to the inferior vena cava. The rest of the blood volume passes to the fetal liver, joins the portal vein, and passes to the right atrium. As a result, drugs and toxic substances are detoxified by the fetal liver prior to exposure to the fetal brain and heart. The fetal circulation is characterized by high pulmonary vascular resistance, low systemic vascular resistance (including the placenta), and right-to-left cardiac shunting via the foramen ovale and ductus arteriosus. As such, the majority of the blood bypasses the fetal lungs. The blood is pumped from the fetal left ventricle through the body to the internal iliac arteries where it passes through the umbilical arteries back to the placenta to be detoxified and reoxygenated.

Drug Transfer

Maternal-fetal exchange of most drugs and other substances with molecular weights of less than 1,000 Da occurs primarily by diffusion. The rate of diffusion and peak levels in the fetus depend on maternal-to-fetal concentration gradients, maternal protein binding, molecular weight of the substance, lipid solubility, and the degree of ionization of that substance. The maternal blood concentration of a drug is normally the primary determinant of how much drug will ultimately reach the fetus. The high molecular weight and poor lipid solubility of nondepolarizing neuromuscular blocking drugs result in minimal transfer of these drugs across the placenta.^{16–23} Succinylcholine has a low molecular weight but is highly ionized and therefore does not readily cross the placenta unless given in very large doses.^{13–15} Thus, during administration of a general anesthetic for cesarean delivery, the fetus/neonate is not paralyzed. If paralysis is desired, for example, during fetal surgery, muscle relaxants must be injected directly into the umbilical vein. Both heparin and glycopyrrolate have minimal placental transfer because they are highly charged.⁵² Placental transfer of volatile agents,^{24–30} benzodiazapines,^{257–60} local anesthetics,^{42–51} and opioids^{31–41} is facilitated by the relatively low molecular weights, neutral charge, and relative lipophilicity of these drugs.

Fetal blood is more acidic than maternal, and the lower pH creates an environment where weakly basic drugs such as local anesthetics can cross the placenta as a nonionized molecule and become ionized in the fetal circulation. Because the newly ionized molecule has more resistance to diffusion back across the placenta, the drug can accumulate in the fetal circulation and reach levels higher than the maternal blood. This process is called “ion trapping.” During fetal distress (lower pH in the fetal circulation), higher concentrations of weakly basic drugs, such as local anesthetics, can be trapped. High concentrations of local anesthetics in the fetal circulation decrease neonatal neuromuscular tone. Extremely high levels such as those associated with unintended maternal intravascular local anesthetic injection result in a variety of fetal effects that include bradycardia, ventricular arrhythmias, acidosis, and severe cardiac depression.

Fetal Liver Function and Drug Metabolism

The anatomy of the fetal circulation helps to decrease fetal exposure to potentially high concentrations of drugs in umbilical venous blood. Approximately 75% of umbilical venous blood initially passes through the fetal liver, which may result in significant drug metabolism by the fetal liver before the drug reaches the fetal heart and brain (first-pass metabolism). Fetal/neonatal enzyme activities are less developed than those of adults, but most drugs that cross the placenta can be metabolized. In addition, drugs entering the fetal inferior vena cava via the ductus venosus are initially diluted by drug-free blood returning from the fetal lower

extremities and pelvic viscera of the fetus. These anatomic characteristics of the fetal circulation markedly decrease fetal plasma drug concentrations compared to maternal concentrations. Although fetal liver function is not yet mature, coagulation factors are synthesized independent of the maternal circulation. These factors do not cross the placenta and their serum concentrations increase with gestational age. However, fetal clot formation in response to tissue injury is less robust in comparison to adults.

Anesthetic Toxicity in the Fetus

All general anesthetic drugs cross the placenta. Although there is no clear evidence for toxicity of specific anesthetic drugs in humans, there is concerning animal data in rodents and primates suggesting that prolonged exposure to general anesthetic drugs including inhaled anesthetics,¹²⁷ propofol,¹²⁸ and ketamine¹²⁹ induce inappropriate neuronal apoptosis that is associated with long-lasting behavioral abnormalities in animals including primates. Although these preclinical results are concerning, it is not clear whether or when these drugs might cause toxicity in humans as the critical period of rapid synaptic development extends from the prenatal period through 2 years of postnatal life.

Efforts to elucidate the neurotoxicity of anesthetic agents on the human developing brain has been far more complicated. There exist methodologic limitations in the face of ethical challenges to designing a randomized controlled trial that could address this central question. Although retrospective human studies have suggested a dose-dependent association between multiple exposures in early childhood and subsequent learning disability,¹³⁰ the effects of anesthetic drug exposure often cannot be distinguished from the underlying disease process or indication for surgery. Furthermore, observational studies do not account for the timing or duration of anesthesia or surgery type, preventing any conclusions on causality from being drawn.

There are no data specifically assessing any association of anesthetic exposure in utero in human fetuses with postnatal neurodevelopmental outcomes. Numerous studies have assessed whether pregnant women undergoing nonobstetric surgery are at an enhanced risk for adverse obstetrical outcomes. Taken together, the most reliable findings suggest a higher rate of spontaneous abortion, preterm delivery, and cesarean section.¹²⁵

Certain lower abdominal or lower extremity procedures can be performed under spinal anesthesia in young infants. The General Anesthesia Compared to Spinal Anesthesia trial¹³¹ is a large multinational trial of children less than 60 months postmenstrual age who were randomly assigned to have awake regional or general anesthesia for hernia surgery. There was no difference in neurodevelopmental outcome between groups at 2- or 5-year follow-up providing some reassurance that a short exposure to general anesthesia does not cause neurodevelopmental damage.¹³²

The U.S. Food and Drug Administration released a safety communication update on April 27, 2017, that touched on potential fetal effects of general anesthesia exposure. The statement verified that pregnant women only have surgery and anesthesia when medically necessary and that exposures are usually less than 3 hours. The advisory stated that pregnant women should not delay or avoid necessary surgeries or procedures during pregnancy as doing so can negatively affect themselves and their infants. The U.S. Food and Drug Administration MedWatch program is available to follow reports of adverse effects.¹³³

As current efforts are attempting to increase the reproducibility and clinical relevance of animal studies and to identify neuroprotective strategies for the immature human brain, it is important to remember that no clear evidence for toxicity of a specific anesthetic drug has been demonstrated so far. Therefore, should the need for general anesthesia arise during pregnancy, the most reasonable anesthetic regimen is one that uses the lowest effective concentration for the shortest amount of time possible. Dexmedetomidine and opioids are the only drugs in clinical use for sedation and anesthesia that have not shown to cause neurodegeneration in animal models.¹³⁴ Although not sufficient for general anesthesia alone, they may become increasingly utilized as adjuvants to offset the required dose of anesthesia in pediatric or nonobstetric surgery.

Fetal Neurophysiology

Fetal Pain

The gestational age at which the fetus can feel pain is highly controversial. The experience of pain requires two conditions: (1) nociception and (2) perception with emotional response. Afferent sensory fibers required for nociception are in place and a functional spinal reflex is present by 20 weeks' gestation ([Figure 45.8](#)).¹³⁵ The second requirement for the experience of pain, perception with emotional response, is much more difficult to establish. In the verbal patient, pain is established by self-report. In the nonverbal, it is measured with observation of complex behaviors thought to be representative of emotional response such as grimace. Neither measurement is practical or necessarily representative in the fetus because of coincident development of motor and intermediary circuitry.

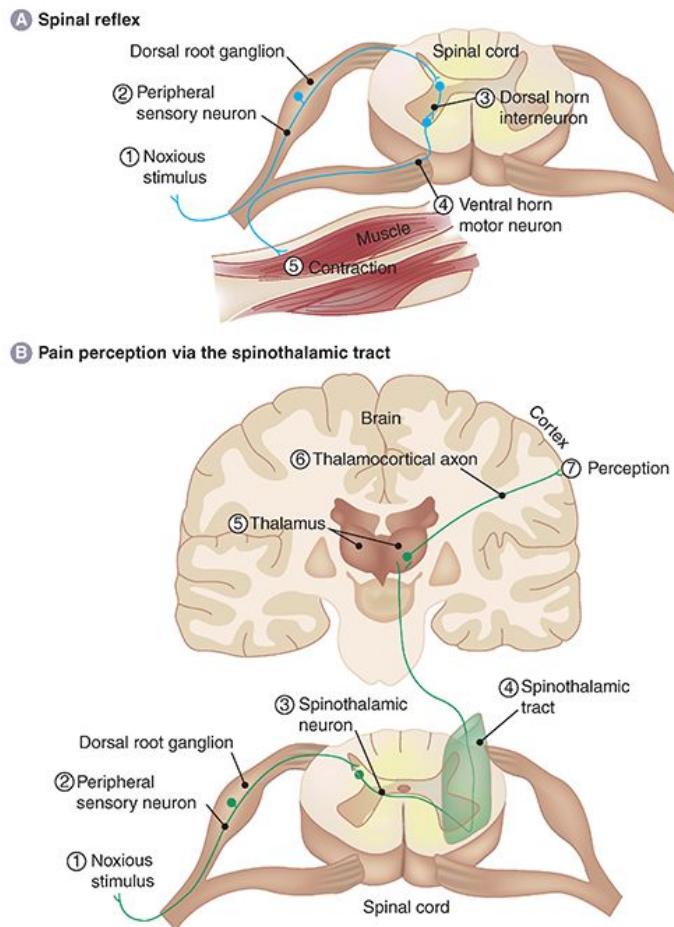


FIGURE 45.8 Spinal reflex and pain perception pathways. **A**, Spinal reflex responses to noxious stimuli occur early in fetal development before cortical connections are functional. **B**, Later in fetal development, a noxious stimulus will activate a peripheral sensory neuron that projects to neurons that form the spinothalamic tract. These neurons in turn project to neurons in the thalamus. Thalamic neurons project to neurons in the subplate zone and the somatosensory cortex. This sequence is the anatomic basis for nociception, the sequence of neuronal events that lead to the conscious perception of pain. The functional circuitry required for apprehension of pain is likely to be present between 20 and 30 weeks' gestation. *Modified from Lowery CL, Hardman MP, Manning N, et al. Neurodevelopmental changes of fetal pain. Semin Perinatol. 2007;31(5):275-282. Copyright © 2007 Elsevier. With permission.*

In humans, after about 2 to 3 months of age, pain can be both apprehended and comprehended. Comprehension requires a relationship with the object. The fetus can likely not comprehend, but only apprehend. Consciousness requires certain anatomic structures to be in place and functional. The neural circuitry that is required for apprehension includes thalamocortical pathways (see [Figure 45.8](#)). The subplate

zone contains the earliest cortical cells and is partially a transient compartment that is required for normal cortical maturation. There is thalamic fiber penetration of an outer layer of brain cells, which stimulate development of the subplate zone by 11 weeks' gestation. Most nociceptive pathways connect from the thalamus to the subplate zone by gestational week 17.¹³⁶ Maturation of the primary somatosensory cortex continues into neonatal life. Evidence for the functionality required for consciousness, thought to be represented by certain electroencephalogram rhythms that are mediated by subcortical integration of cortical and subcortical processes are present from 20 weeks' gestation.¹³⁷ Somatosensory evoked potentials can be recorded from the fetal cerebral cortex at 29 weeks' gestation.¹³⁸ As such, the functional circuitry required for apprehension of pain is likely to be present between 20 and 30 weeks' gestation (**Table 45.5**). These details are of concern to the anesthesiologist to inform decisions about anesthesia for fetal surgery and whether and at what point a live fetus requires anesthesia and analgesia prior to abortion.

TABLE 45.5

Anatomic and functional development of nociception and pain perception^a

Anatomic/functional characteristic	Description	Gestational age (weeks)
Peripheral cutaneous sensory receptors	Perioral cutaneous sensory receptors	7.5
	Palmar cutaneous sensory receptors	10-10.5
	Abdominal cutaneous sensory receptors	15
Spinal cord	Spinal reflex arc in response to nonnoxious stimuli	8
	Neurons for nociception in dorsal root ganglion	19
Thalamic afferents	Thalamic afferents reach subplate zone	20-22
	Thalamic afferents reach cortical plate	23-24
Cortical function ^b	Somatosensory evoked potentials with distinct, constant components	29
	First electrocardiographic pattern denoting wakefulness and active sleep	30

^aAdapted with permission from Lee SJ, Ralston HJ, Drey EA, et al. Fetal pain: a systematic multidisciplinary review of the evidence. *JAMA*. 2005;294(8):947-954. Copyright © 2005 American Medical Association. All rights reserved.

^bBest evidence of functional thalamocortical connections required for conscious perception of pain

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Physiology and Pharmacology of the Elderly

Andrea Girnius • Pamela Flood

The US population is aging, and the percentage of patients older than 65 years is increasing rapidly. The 2010 US census found that patients older than the age of 65 years comprised 13% of the U.S.

population, or 40,300,000 people.¹ The United States Census Bureau estimates that by 2060, the number of patients older than age 65 years will double from their 2018 levels, and their proportion of the population will rise from 16% in 2018 to 23% in 2060. As elderly people are more likely to require invasive procedures, the number presenting for surgery can only be expected to increase. It is important that anesthesiologists understand the differences in pharmacology and physiology in elderly patients in order to be able to properly use anesthetic and analgesic drugs and compensate for aging-related functional decline in major organ systems. Some fortunate individuals remain physically vigorous until very late in life, whereas others deteriorate physically at a younger age. The cumulative effects of smoking, alcohol, and environmental toxins can accelerate the deterioration of aging in exposed individuals. Thus, it is not surprising that variability in physiology increases throughout life.² Increased physiologic variability results in potentially decreased physiologic reserve and increased pharmacokinetic and pharmacodynamic variability in elderly subjects.³ The clinical result of this increased variability is an increased incidence of adverse drug reactions in elderly patients.⁴ Thus, elderly patients require more careful attention to drug titration and overall physiologic parameters.

Aging and the Cardiovascular System

Increasing age is associated with increasing cardiac morbidity. Aging is associated with an increasing prevalence of cardiovascular disease and decreasing cardiovascular functional reserve.⁵ Heart failure is the most frequent cause of hospitalization in patients older than 65 years of age. However, it is important to separate the cardiovascular effects of aging from those of common diseases with increased prevalence in the elderly, such as atherosclerosis, hypertension, and diabetes mellitus. The decline in cardiac function that occurs with aging in the healthy individual appears to be related, in part, to decreasing functional demand. Indeed, when exercise and low-calorie diet are maintained into the later decades, the decline in cardiovascular function is markedly attenuated.⁶ Aging is associated with the development of heart failure, particularly in women in whom its prevalence increases greater than twofold from age 65 to 69 (6.6%) to age 85 years (14%).⁷ Almost half the people presenting with heart failure appear to have normal left ventricular systolic function, a phenomenon that is more common in women.⁸ It has been suggested that cardiovascular function is directly related to skeletal muscle mass. Aging also has discrete effects on the heart, large vessels, endothelial function, cardiac conduction system, and the cardiovascular autonomic response (**Figure 46.1**).⁶

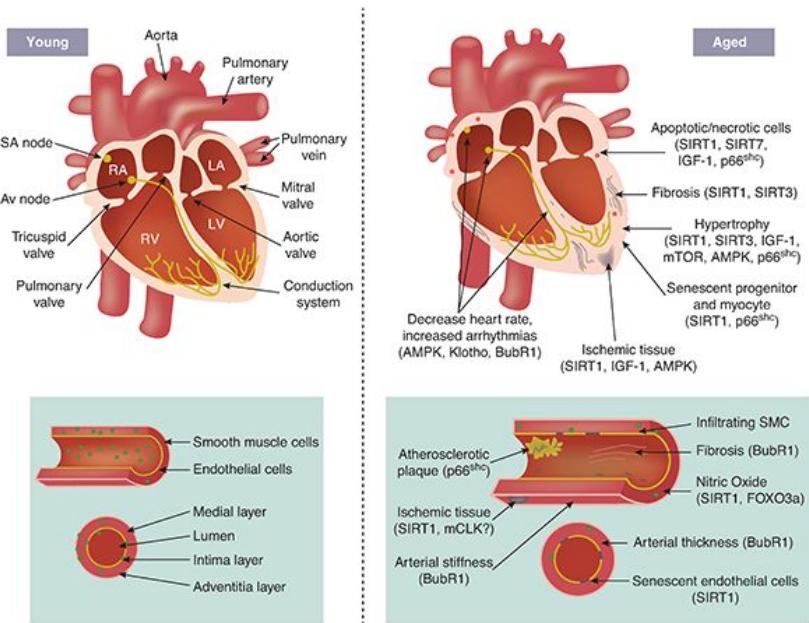


FIGURE 46.1 Age-dependent changes to cardiovascular tissues. Both the heart and vasculature undergo numerous alterations during aging as a result of deregulation of molecular longevity pathways, leading to compromised function. Important functional changes include arterial hypertrophy resulting in increased afterload, ventricular hypertrophy resulting in elevated systolic blood pressure, loss of cells in the electrical conduction system predisposing to arrhythmia, and loss of sensitivity to catecholamines resulting in reduced maximal heart rate and heart rate variability. Abbreviations: AMPK, 5' adenosine monophosphate-activated protein kinase; Av, atrioventricular; BubR1, budding uninhibited by benzimidazole-related 1; FOXO3a, forkhead box O3a; IGF-1, insulin like growth factor 1; LA, left artery; LV, left ventricle; mLCK, myosin light chain kinase; mTOR, mammalian target of rapamycin; p66shc, p66 SHC-transforming protein 1; RA, right artery; RV, right ventricle; SIRT1, NAD-dependent deacetylase sirtuin 1; SIRT3, NAD-dependent deacetylase sirtuin 3; SIRT7, NAD-dependent deacetylase sirtuin 7; SMC, smooth muscle cell. Adapted with permission from North BJ, Sinclair DA. *The intersection between aging and cardiovascular disease*. Circ Res. 2012;110(8):1097-1108. Illustration credit: Cosmocyte/Ben Smith. Copyright © 2012 American Heart Association, Inc.

Heart

The heart increases in size during aging as a result of concentric ventricular hypertrophy. This occurs in response to the increase in left ventricular afterload. This increase in afterload occurs as the result of fibrosis and endothelial damage, which increases arterial stiffness and reduces the capacity for nitric oxide-induced vasodilation. Hypertrophy of cardiac myocytes accounts for a 30% increase in left ventricular wall thickness. Meanwhile, the number of cardiac myocytes is decreased due to necrosis and apoptosis. These changes result in an increased incidence of hypertension that can be followed by reduced cardiac function. Initially, sympathetic hyperactivity compensates and systolic function is preserved. However, with chronic stimulation, β -adrenergic receptors become less responsive and contractility is reduced.⁹ Despite these changes, resting systolic function tends to be well preserved in healthy individuals. However, the heart rate response to strenuous exercise is diminished.

Diastolic dysfunction and heart failure with preserved ejection fraction are now recognized as a major contributor to cardiovascular disease in the elderly population. The prevalence of heart failure with preserved ejection fraction is increasing as the population ages and currently accounts for 50% of patients with clinical heart failure. It is exacerbated by several coexisting diseases, such as systemic hypertension, coronary artery disease, cardiomyopathy, aortic stenosis, atrial fibrillation, diabetes, and chronic renal disease ([Table](#)

46.1).^{7,10} The impairment in diastolic function is likely due to an age-related increase in cardiac connective tissue that, when combined with ventricular hypertrophy, increases wall stiffness and reduces diastolic compliance.¹¹ Ventricular filling in the elderly is especially dependent on active diastolic relaxation. In this process, calcium is removed from troponin C binding sites, triggering the dissociation of actin and myosin, thus facilitating isometric relaxation. Active diastolic relaxation uses approximately 15% of the energy consumed during the cardiac cycle. This process is significantly impaired in the elderly and exacerbates the adverse effects of ventricular hypertrophy on diastolic filling. Therefore, the elderly heart is markedly dependent on the atrial “kick” for adequate ventricular preload. It is estimated that atrial contraction contributes approximately 30% of ventricular filling in the elderly versus 10% in younger individuals. Because passive ventricular filling is impaired by reduced ventricular compliance and because of the importance of atrial contraction, ventricular filling is typically not complete until very late in diastole. Tachycardia and the resulting shortened diastolic intervals will markedly decrease ventricular preload in the elderly. Atrial fibrillation is a common rhythm in the elderly in which the benefit of atrial contraction is lost. As previously noted, loss of coordinated atrial contraction is particularly important in elderly patients. Perioperative events that reduce venous return, such as hypovolemia, positive pressure ventilation, and increased venous capacitance, may be accompanied by significant decreases in cardiac output. Conversely, excessive perioperative increases in blood volume or decreases in contractility can precipitate congestive cardiac failure.

TABLE 46.1

Diseases commonly encountered in the elderly that are associated with diastolic dysfunction

Systemic hypertension

Coronary artery disease

Cardiomyopathy

Aortic stenosis

Atrial fibrillation

Diabetes

Chronic renal disease

It is difficult to identify diastolic dysfunction during routine clinical evaluation. Dyspnea in the elderly is nonspecific and may indicate congestive heart failure, pulmonary disease, or both. Furthermore, routine preoperative echocardiographic indices of cardiac function such as left ventricular ejection fraction will fail to identify diastolic dysfunction. However, diastolic filling can be evaluated by comparing Doppler echocardiographic measurements of mitral valve inflow velocities during the early and late (atrial contraction) phases of diastole, Doppler measurements of pulmonary vein inflow during systole and diastole, and tissue Doppler measurements of the mitral valve annulus.

Large Vessels

Structural changes in the large vessels are an important element of the aging process and contribute significantly to the age-related changes in the heart.⁵ The large vessels become elongated, tortuous, and dilated in the elderly. Their intima and media thicken, causing them to be less distensible. The normal cushioning function of the large vessels is impaired; causing accelerated and enhanced pulse wave propagation. In the elderly, the pulse wave from systolic contraction is reflected back relatively quickly from the peripheral circulation and increases systolic pressure. In young adults, the reflected pulse wave generally has lower amplitude and its return from the peripheral circulation is delayed such that diastolic rather than systolic pressure is augmented. Thus, in the elderly, both systolic pressure and pulse pressure are increased and left ventricular afterload is elevated. In contrast, diastolic pressure tends to be lower in the elderly than in younger individuals. Isolated systolic hypertension accounts for a large percentage of clinical hypertension in the elderly. All of the aforementioned age-related vascular structural changes are accelerated in the presence of hypertension or atherosclerosis.

Endothelial Function

The vascular endothelium is an important regulator of vasomotor response, coagulation, fibrinolysis, immunomodulation, and vascular growth and proliferation. Endothelial dysfunction is an important element in the early pathogenesis of atherosclerosis, diabetes mellitus, and systemic hypertension.¹² Aging is associated with altered endothelial structure and function, even in the absence of disease. Endothelial dysfunction is accelerated by smoking, diabetes, hypertension, and hyperlipidemia. Endothelial nitric oxide is a key mediator of vascular relaxation. In the elderly, the bioavailability of endothelial nitric oxide is decreased due to both decreased production and increased degradation. This is due in part to alterations of level and activity of key enzymes and substrates as well as increased levels of reactive oxygen species mediated by chronic inflammation.⁵ Furthermore, the vasodilator response to nitric oxide of the adjacent vascular smooth muscle is reduced. Vasodilator responses to β_2 agonists and vasoconstrictor responses to α -adrenergic stimulation are similarly attenuated in the elderly. Thus, age-related endothelial dysfunction can be characterized as a decrease in the ability of the endothelium to dilate or contract blood vessels in response to physiologic and pharmacologic stimuli.

Conduction System

There are several important age-related structural and functional changes in the cardiac conduction system.¹³ The sinoatrial node undergoes progressive fibrosis over time so that the proportion of pacemaker cells decreases from 50% in late childhood to less than 10% at 75 years. The atrioventricular node, and conduction bundles similarly become infiltrated with fibrous and fatty tissue. These changes are responsible for the increased incidence of first- and second-degree heart block, sick sinus syndrome, and atrial fibrillation in the elderly. The development of atrial fibrillation is also facilitated by left atrial enlargement, which typically accompanies aging in otherwise healthy individuals. The prevalence of atrial fibrillation doubles with each decade. Eighty-four percent of patients with atrial fibrillation are older than 65 years. Elderly patients also experience an age-related increase in the prevalence, frequency, and complexity of ventricular ectopy and ventricular arrhythmias, even in the absence of structural heart disease.¹³

Autonomic and Integrated Cardiovascular Responses

Aging is associated with increased norepinephrine release into the circulation and deficient catecholamine reuptake at nerve endings. The resulting elevated circulating concentration of norepinephrine generates chronically increased adrenergic receptor occupancy. However, the cardiovascular response to increased adrenergic stimulation is attenuated by the decreased number of the β -adrenergic receptors in the elderly myocardium, the downregulation of postreceptor signaling pathways, and the reduced contractile response of the myocardium.¹¹ Alterations in the mechanism by which the receptor binding is coupled to cyclic adenosine monophosphate also contribute to the decreased chronotropic and inotropic response of elderly patients to β -adrenergic drugs. The response to exogenously administered β agonists, such as isoproterenol, is similarly attenuated. Receptor downregulation is responsible for the age-related decline in maximum heart rate during exercise. Indeed, receptor downregulation in the elderly makes their baseline cardiovascular function similar to that of a younger individual who has received β -adrenergic antagonists.

Orthostatic hypotension is common in the elderly. The prevalence is reported as 15% in patients aged 65 to 69 years but increases to 26% in patients older than age 85 years.¹⁴ It is associated with syncope, falls, cognitive decline, and increased mortality. Orthostatic hypotension is more common in patients who are hypertensive at baseline. Several age-related changes contribute to the increase in orthostatic hypotension, including impaired baroreceptor reflexes, attenuated peripheral vasoconstriction, hypovolemia, and salt depletion. These factors can be the result of iatrogenic antihypertensive and diuretic administration or increased atrial natriuretic peptide release. It is difficult to separate the effects of aging per se from those of age-related chronic increases in systolic pressure and iatrogenic treatment of elevated systolic pressure. Straining against a closed glottis (Valsalva maneuver) typically produces a decrease in venous return and cardiac output. The normal baroreceptor response to this maneuver includes an increase in heart rate and peripheral vascular tone and restoration of blood pressure. However, this response is markedly attenuated in

the elderly.¹⁴ Similarly, age-related impairment of baroreceptor responses makes hypotension more likely after the initiation of positive pressure ventilation, particularly in the presence of hypovolemia. Neuraxial local anesthetic-induced sympathetic blockade is also more likely to be accompanied by hypotension in the presence of an impaired baroreceptor response. The relationship between medications and orthostatic hypotension is important to consider, as many elderly patients are on multiple antihypertensive agents. The Irish Longitudinal Ageing Study found that antidepressants and β blockers were associated with orthostatic hypotension, and hypnotics and sedatives worsened preexisting orthostatic intolerance.¹⁵ Antihypertensive drugs that did not act through β -adrenergic blockade were not associated with orthostatic hypotension with the possible exception of diuretics. Multiple studies have demonstrated that patients on multiple antihypertensives experience more orthostatic hypotension, but other studies have not found this association. The Systolic Blood Pressure Intervention Trial found that the intensive treatment group had significantly better cardiovascular outcomes but experienced less orthostatic hypotension.^{14,16} These findings should be considered in the mobilization of elderly patients who may have received these drugs in the perioperative period.

Anesthetic and Ischemic Preconditioning in the Aging Heart

It is now recognized that, under certain circumstances, exposure to volatile anesthetics (anesthetic preconditioning) or several brief periods of ischemia (ischemic preconditioning) may enhance tolerance to subsequent ischemia, enhance cardiac function, and reduce infarction size.¹⁷ Because the incidence of atherosclerosis and coronary artery disease is age related, the elderly would seem to be most likely to benefit from a preconditioning strategy. However, both anesthetic and ischemic preconditioning may be markedly attenuated in the elderly, potentially explaining the difficulty of translating promising preclinical results to treatment.^{18,19} Furthermore, potent volatile drugs may induce significant cardiovascular depression in this age group. Therefore, the clinical utility of preconditioning strategies in this age group is uncertain.

Aging and the Respiratory System

The respiratory system undergoes a multifactorial decline in functional reserve with aging (**Tables 46.2** and **46.3**).²⁰ Under normal circumstances, this decrease in respiratory function is not associated with significant limitation of daily activity. However, decreased respiratory reserve may be unmasked by illness, surgery, anesthesia, and other perioperative events. Common respiratory diseases and the effects of smoking and environmental pollution frequently exacerbate the decline in respiratory function with aging. The anticipation and amelioration of their effects is critically important to anesthetic management in the elderly, as age greater than 65 years has been shown to be an independent risk factor for postoperative respiratory complications, contributing significantly to perioperative mortality in this population.²¹

TABLE 46.2

Intrinsic and extrinsic events that influence the respiratory system during aging

Intrinsic to the aging process	Environmental, behavioral, and disease related
Decreased bronchiolar caliber	Industrial and environmental pollution
Decreased alveolar surface area	Smoking
Increased lung collagen content	General deconditioning
Decreased lung elastin content	Coexisting disease
Kyphoscoliosis	
Increased thoracic cage rigidity	
Decreased diaphragmatic strength	

TABLE 46.3

Functional consequences of the intrinsic and extrinsic events that influence the respiratory system during aging

Decrease in lung elastic recoil
Increase in lung compliance
Decrease in oxygen diffusing capacity
Premature airway closure causing V/Q mismatch and increased alveolar-to-arterial oxygen gradient
Small airway closure and gas trapping
Decreased expiratory flow rates

Abbreviation: V/Q, ventilation-perfusion.

Respiratory System Mechanics and Architecture

The chest wall becomes less compliant with aging, presumably related to changes in the thoracic skeleton and a decline in costovertebral joint mobility. These changes in and of themselves produce a restrictive functional impairment. The noncompliant thoracic cage makes intercostal muscle activity less efficient. Therefore, the diaphragm and abdominal muscles assume a greater role in tidal breathing. However, diaphragmatic function also declines with age, predisposing the elderly to respiratory fatigue when required to significantly increase minute ventilation. Diaphragmatic strength is decreased likely due to atrophy and relative loss of large myelinated muscle fibers. It also occupies a flatter position and therefore has a less favorable mechanical advantage.²² These changes increase the risk of respiratory insufficiency in the setting of high regional anesthesia.

The lungs become more distensible with age due to a loss of lung elasticity, which leads to decreased lung recoil. Changes in surfactant function contribute to age-related changes in lung compliance. The net result of these changes in the elastic properties of the lung and chest wall is an increase in intrapleural pressure that significantly impacts respiratory function. Intrapleural pressure is a critical determinant of small airway caliber. Increased intrapleural pressures increase the tendency for small airway collapse to occur, causing air trapping and/or expiratory airflow limitation.²²

Lung Volumes and Capacities

Vital Capacity

Vital capacity (VC) is the volume generated when a maximal inspiration is followed by a maximal expiration. There is a progressive loss of VC with aging that results from increased chest wall stiffness, decreased lung elastic recoil, and decreased respiratory muscle strength.

Residual Volume

The residual volume (RV) is the volume remaining in the lungs after a maximal expiration. In young individuals, the RV is determined primarily by ability of the expiratory muscles to overcome the elastic recoil properties of the lung and chest wall. However, in the elderly, dynamic small airway closure also limits expiration and increases the RV. Therefore, aging is associated with a progressive increase in RV of up to 10% per decade ([Figure 46.2](#)).²³

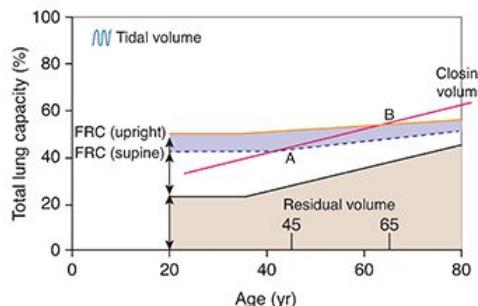


FIGURE 46.2 Effect of aging on lung volumes. Functional residual capacity (FRC) increases with age as a result of increasing residual volume. Closing volume also increases with age and exceeds FRC in the upright

position around age 65 years and in the supine position at age 45 years. These changes lead to ventilation perfusion mismatch and shunt, resulting in reduced resting Po_2 with age. *Reprinted by permission from Springer: Sprung J, Gajic O, Warner DO. Review article: Age related alterations in respiratory function—anesthetic considerations. Can J Anaesth. 2006;53(12):1244-1257. Copyright © 2006 Springer Nature. Modified with permission from Zaugg M, Lucchinetti E. Respiratory function in the elderly. Anesthesiol Clin North Am. 2000; 18(1):47-58. Copyright © 2000 Elsevier.*

Total Lung Capacity

Total lung capacity is the sum of the RV and the VC. The combined effect of the decline in VC and increase in RV is that the total lung capacity remains relatively constant with aging.

Functional Residual Capacity

The functional residual capacity (FRC) is the volume remaining in the lungs at the end of a normal expiration. The FRC is the volume at which the elastic recoil forces of the lung and chest wall are at equilibrium. The opposing recoil forces of the lung and chest wall generate the subatmospheric intrapleural pressure. Aging is associated with a decreased elastic recoil force of the lungs, which leads to a progressive increase in FRC. However, the increase in FRC is less than would be predicted from the change in lung elastic recoil alone. This is because the increased stiffness of the chest wall counteracts the increase in lung volume.

Closing Capacity

Spontaneous airway closure may occur in small airways (<1 mm) whose caliber is determined by their transmural pressure. Airway closure typically occurs in dependent areas of the lung where the surrounding intrapleural pressure is likely to be greater. In young adults, airway closure occurs only at low lung volumes (approximately 10% of VC). Thus, airway closure is unlikely during normal tidal breathing. However, as intrapleural pressure increases with age, airway closure occurs at progressively greater lung volumes. Indeed, in the elderly, airway closure occurs at approximately 40% of the VC, reflecting lung volumes that exceed FRC. Although the FRC increases by up to 3% per decade, closing capacity increases at a greater rate. Thus, gas exchange impairment due to shunting in regions of airway closure is typical in the elderly during normal tidal breathing. The supine position is associated with a decrease in FRC when compared to the standing position. Therefore, the supine position makes airway closure during normal tidal breathing more likely. Indeed, airway closure may occur during tidal breathing as early as the mid-40s in the supine position.²⁴

Expiratory Flow

There is a progressive decline in forced exhaled volume in 1 second and forced VC with age that is independent of smoking or environmental exposure. Age-related loss of lung elastic recoil predisposes to dynamic airway collapse during forced expiratory maneuvers. Expiratory muscle strength also declines with age.

Diffusing Capacity and Alveolar-to-Arterial Oxygen Gradient

Gas exchange efficiency declines with aging as a result of increasing intrapulmonary shunting and decreasing lung diffusing capacity. The result is a linear decline in resting supine Pao_2 between early adulthood and 65 years of age (Figure 46.3).²⁵ The cause of this decline is multifactorial. Small airway closure causes ventilation-perfusion mismatch and shunting. Cardiac output is often decreased in the elderly to the extent that mixed venous oxygen tension is decreased. Thus, even modest amounts of shunting may produce a significant decrease in Pao_2 because of the contribution of desaturated venous blood. The diameter of the alveolar ducts is increased and their respective alveoli are wider and shallower. These architectural changes significantly reduce alveolar surface area. As a result, diffusing capacity for carbon monoxide may decline by up to 50% between early adulthood and 80 years of age.

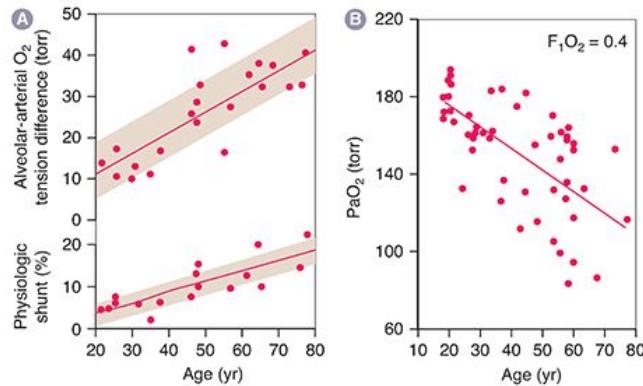


FIGURE 46.3 Effect of aging on gas exchange. **A**, The change in alveolar/arterial oxygen tension with age (shunt fraction or percent shunt). **B**, Relationship of PO₂ with age during spontaneous breathing of 40% oxygen and 60% nitrous oxide under general anesthesia with enflurane. *Reprinted with permission from Wahba WM. Influence of aging on lung function—clinical significance of changes from age twenty. Anesth Analg. 1983;62(8):764-776. Copyright © 1983 International Anesthesia Research Society.*

Upper Airway Protective Reflexes

Cough effectiveness is reduced in the elderly because of diminished reflex sensitivity and impaired muscle function. The mechanisms of cough reflex impairment include desensitization of airway epithelial irritant receptors and impaired swallowing.²⁰ Cough reflex attenuation is associated with an increased incidence of aspiration pneumonia. Smoking further exacerbates the situation by causing airway sensory nerve neuropeptide depletion and inhibition of C fiber transmission by nicotine in the lower respiratory tract.²⁶ Coexisting medical conditions that are associated with cough reflex suppression include stroke, laryngectomy, and Parkinson disease. General anesthetics inhibit the cough reflex through inhibition of central respiratory neurons.²⁷ Caution is needed during intubation and extubation of the elderly, especially those patients with additional risk factors for impaired airway protection.

Control of Breathing, Chemoreceptors, and Integrated Responses

The reflex cardiorespiratory responses to hypoxia and hypercarbia are mediated via central and peripheral chemoreceptors. The increases in heart rate and minute ventilation in response to elevations in PaCO₂ or decreases in PaO₂ are markedly attenuated in the elderly. The attenuated ventilatory response is multifactorial and reflects decreased peripheral chemoreceptor sensitivity, reduced respiratory muscle activity, decreased respiratory mechanical efficiency, and general respiratory deconditioning. These important protective reflexes are further attenuated by the administration of opioids and sedative/hypnotic drugs. Thus, the elderly are at particular risk from life-threatening respiratory depression in the perioperative period. Multiple reports have shown that the risk of opioid-induced ventilatory depression is increased in patients aged older than 65 years.^{28,29} Although the risk of respiratory depression from opioids is greater in the elderly, the same is not true for all opioid side effects.

Opioids are a major cause of postoperative nausea and vomiting in young and middle-aged patients, with a nearly fourfold increased risk over older patients in one study.³⁰ The relationship between age and the incidence of nausea and vomiting is actually inverse unlike most adverse physiologic effects and side effects.^{29,31,32}

Sleep-Disordered Breathing

The incidence of sleep-disordered breathing increases with age, especially in men. It is estimated that approximately 20% of elderly people have clinically significant obstructive sleep apnea.³³ The prevalence of snoring is highest in the seventh decade and is associated with an increased risk of stroke and heart disease. Morbidity associated with sleep apnea includes systemic and pulmonary hypertension, dysrhythmias,

myocardial infarction, stroke, sudden death, and automobile accidents. In addition, obstructive sleep apnea doubles the risk for postoperative delirium (POD) in the elderly.^{34,35}

The Coagulation System in the Elderly

The coagulation system undergoes changes with age. The plasma concentration of many coagulation factors, including factors V, VII, VIII, and IX, as well as von Willebrand factor is increased. Data are less conclusive regarding anticoagulant proteins such as protein C, protein S, and antithrombin. The overall balance of these changes is a relatively procoagulant state. In addition, multiple comorbidities that accumulate with age, including diabetes and cancer, confer a prothrombotic state. The effects of these comorbidities are difficult to distinguish from the normal aging process.³⁶

The incidence of venous thromboembolism (VTE) and pulmonary embolism increases with age. Patients younger than 65 years experienced 231 events per 100,000 people, whereas those 65 years and older experienced 1,382 VTE events per 100,000 people.³⁷ Pulmonary embolism accounts for an increasing percentage of VTE events as age increases.³⁸ The incidence of VTE overall is increasing and is expected to more than double by 2050. The elderly population will likely be disproportionately affected by this trend.³⁷ Even in patients on vitamin K antagonists, there is a higher risk of thrombosis as age increases.³⁹

As the coagulation system is altered with age, perioperative hemostasis may be expected to be altered as well. A study on coagulation parameters in elderly (>80 years) and younger patients (<60 years) undergoing cardiac surgery revealed that, based on thromboelastogram data, the elderly patients were relatively hypocoagulable before their surgery and had greater blood loss and transfusion requirements than the younger patients.⁴⁰ This contradicts the data showing an increase in most clotting factors and VTE incidence with age. In addition, elderly patients are more likely to be on anticoagulants at baseline (eg, for atrial fibrillation or history of VTE). The effect of aging on hemostasis and coagulation is not necessarily straightforward, and elderly patients may be predisposed to both increased thrombosis and increased bleeding perioperatively.

Thermoregulation in the Elderly

There is ample evidence that hyperthermia and hypothermia in the elderly are poorly tolerated and that extreme cold and heat stress are associated with increased mortality compared to younger individuals.⁴¹ Several physiologic alterations contribute to this, including decreased sweating and alterations in skin blood flow in response to thermal challenge and may be due to reduced physiologic reserve.⁴² Although there are clear physiologic alterations in temperature regulation in the elderly, the observed greater susceptibility to thermal stress in the population may also be related to underlying socioeconomic conditions, general fitness, activity levels, and the effects of coexisting disease in the elderly.

Resting Core Temperature

Aging is associated with a greater variability in core temperature. It is estimated that up to 10% of people older than 65 years of age have early morning core temperatures of less than 35.5°C (**Table 46.4**).⁴¹ The regulation of body temperature is complex and involves many systems including the cardiovascular and respiratory systems. As discussed earlier, these systems have reduced function with advancing age, resulting in a negative impact on the control of body temperature. Some changes such as those that occur in the musculoskeletal system can be slowed or even prevented by exercise partially preventing decrements in thermoregulatory functions. Some deficits such as skin changes and metabolic slowing are unavoidable.⁴²

TABLE 46.4

Factors associated with reduced resting core temperatures in the elderly

Neurologic disease
Diabetes
Low body weight
Lack of self-sufficiency
Consumption of less than two meals per day

Smoking

Alcohol consumption

In old age, circadian rhythms break down and organisms lose their ability to adapt to the periodic environment. Sleep disorders are frequently observed in older people and are believed to be caused, at least partly, by changes in the circadian system.^{43,44}

Response to Cold Stress

The elderly do not tolerate cold stress as well as younger people. The usual physiologic response to cold stress is to decrease heat loss by peripheral vasoconstriction and to increase heat production via shivering and nonshivering thermogenesis. Aging is associated with attenuated vasoconstrictor responses to cold.⁴¹ The inability to efficiently conserve heat in the elderly is exacerbated by the age-related decrease in skeletal muscle mass. Loss of skeletal muscle mass is responsible for the age-related decline in basal heat production. It is estimated that resting heat production declines by 20% between the ages of 30 and 70 years. There is a significant gender-related difference in cold stress response in the elderly. Mortality during cold weather is higher in men compared to age-matched women.⁴⁵ It is likely that the higher percentage of body fat and lower surface area-to-mass ratio in females is responsible for their better outcome. The attenuated cold stress responses of the elderly are further diminished by general and regional anesthesia. Perioperative hypothermia is very likely to occur in the elderly patient unless active measures are taken to maintain normothermia.

Gastrointestinal Function in the Elderly

Liver

Although aging is associated with a 25% to 35% decrease in liver mass and a 40% reduction in hepatic blood flow, hepatocellular metabolic function appears to be relatively well preserved throughout life. Protein synthetic function may be diminished in some elderly individuals, particularly those with poor nutritional intake. The resulting reduced serum albumin concentrations affect the bioavailability of highly protein-bound drugs.⁴⁶ On the other hand, the concentration of another important drug-binding protein, α_1 acid glycoprotein, is typically increased in the elderly. Hepatic synthesis of plasma cholinesterase may be diminished, particularly in men, but this is not likely to be clinically important in the absence of concurrent genetic mutation.⁴⁷

Although in vitro data indicates that the function of hepatic enzymes involved in phase I and II metabolism (including the cytochrome P450 enzymes) is maintained,⁴⁶ the reduction in hepatic mass and blood flow is responsible for an in vivo decrease in first-pass metabolism of several drugs that are important in the aging population.⁴⁷ Nondepolarizing neuromuscular-blocking agents such as vecuronium and rocuronium have prolonged effects in the elderly for this reason. Conversely, prodrugs, such as the angiotensin-converting enzyme inhibitor enalapril, codeine, and tramadol, require activation by the liver before they exert their pharmacologic effect. Therefore, the bioavailability of these drugs may be decreased in the elderly.

Gastroesophageal Physiology

With age, both skeletal and smooth muscle in the esophagus hypertrophies, impairing the coordination of peristalsis. Transit of food in the esophagus is not impaired, but transit of liquids is delayed.⁴⁸ Gastric emptying of solid material appears to be relatively normal in the healthy elderly population. However, gastric emptying of liquids may be delayed compared to younger individuals.⁴⁹ Gastroesophageal reflux disease (GERD) is common in the elderly. Recent studies show that most patients with GERD are older than 70 years old. However, this demographic trend may be shifting as more young people are diagnosed with GERD. Therefore, the overall ratio of older-to-younger patients with GERD is decreasing (**Table 46.5**).⁵⁰ The typical symptoms of GERD seen in the younger population (heartburn and regurgitation) are less frequent in the elderly, making diagnosis more difficult.⁵¹ Dysphagia, vomiting, respiratory symptoms, weight loss, and

anemia are more common presenting symptoms in the elderly. Several medications that are commonly prescribed in the elderly population predispose them to GERD by decreasing lower esophageal sphincter tone ([Table 46.6](#)).

TABLE 46.5

Factors that predispose to the increased incidence of gastroesophageal reflux disease in the elderly
Increased prevalence of sliding hiatal hernia
Shortened intra-abdominal segment of the lower esophageal sphincter
Impaired clearance of refluxed acid
Use of medications that reduce lower esophageal sphincter pressure
Decreased esophageal peristalsis pressure

TABLE 46.6

Medications that are commonly administered in the elderly that reduce lower esophageal sphincter tone and predispose to gastroesophageal reflux
Anticholinergics
Antidepressants
Nitrates
Calcium channel blockers
Theophylline

Renal Function in the Elderly

Aging is accompanied by a reduction in renal mass and a decrease in the cortical nephron population. The medullary nephron population is relatively preserved, and age-related vascular changes in the medulla are minimal. Renal blood flow and glomerular filtration rate (GFR) both decline with age.⁵² The average male GFR is 125 mL per minute. This value decreases by approximately 1 mL/min per minute per year after the age of 40 years as a result of the decline in nephron population and hyalinization of cortical afferent arterioles. Despite the significant decline in GFR with aging, the serum creatinine concentration increases minimally because there is also an age-related decrease in skeletal muscle mass. This diminished renal function is sufficient to maintain homeostasis under normal physiologic conditions. However, common perioperative stresses such as hypotension and hypovolemia may unmask the diminished renal reserve, and acute renal dysfunction may manifest.⁵³ Although the elderly individual is able to maintain acid-base balance under everyday physiologic conditions, the response to increased acid loads such as during ischemia and sepsis is attenuated due to impaired renal tubular ammonium secretion.

The elderly are at risk for both free water deficit and free water overload because of impaired renal response. Urine concentrating ability prevents free water loss and is critically dependent on the presence of a hypertonic renal medulla. However, medullary perfusion is relatively increased in the elderly, resulting in a washout of solute and a reduction in osmolality in that region. Thus, the collecting tubules are not exposed to the usual concentration gradient necessary to produce concentrated urine.⁵⁴ Reduced numbers of cortical nephrons also contribute to impaired salt conservation. This suboptimal renal response to dehydration is compounded by age-related deficiencies in thirst mechanisms. Water deprivation is associated with a reduced thirst response in elderly subjects despite significant increases in plasma osmolality.⁵⁵ As a result of these factors, the elderly are at enhanced risk for dehydration and hypernatremia.

The response to free water excess is similarly attenuated in the elderly. This is particularly relevant because the perioperative neuroendocrine stress response is associated with arginine vasopressin (antidiuretic hormone) release and water retention. When combined with iatrogenic hypotonic fluid administration, these factors make the elderly patient particularly susceptible to perioperative free water overload and hyponatremia.

Skeletal Muscle Mass and Aging

Aging is associated with a significant decline in neuromuscular performance. Neuromuscular decline results predominantly from loss of skeletal muscle mass (sarcopenia), which declines by approximately 40% between the ages of 20 and 60 years. By the seventh and eighth decades, maximal voluntary contractile strength is reduced by 20% to 40%. This leads to functional disability, loss of independence, and increased mortality.^{56,57} The decline in muscle function is multifactorial (**Table 46.7**). However, strength losses with aging may be attenuated by continued physical activity, particularly resistance training. Diminished skeletal muscle mass has significant implications for the elderly patient in the perioperative period (**Table 46.8**).

TABLE 46.7

Factors that are thought to be responsible for the significant decrease in lean muscle mass that occurs with aging

Decreased motor neuron innervation
Decreased physical activity
Endocrine shift toward catabolism (reduced insulin-like growth factor 1 secretion)
Decreased androgen (testosterone and estrogen) secretion
Decreased total caloric intake
Decreased protein consumption and protein synthesis
Inflammatory mediators and cytokines (interleukins 1 and 6, tumor necrosis factor)

TABLE 46.8

Perioperative functional consequences of the loss of skeletal muscle mass that typically accompanies aging

Impaired postoperative mobilization and ambulation
Reduced cough effectiveness
Reduced shivering thermogenesis
Altered drug disposition
Reduced neuromuscular functional reserve
Prolonged recovery and hospitalization

Neurophysiology of Aging

The elderly have increased sensitivity to benzodiazepines, opioids, and volatile anesthetic agents. The minimum alveolar concentration of potent volatile anesthetic agents decreases about 6% with each decade. This is likely due to altered ion channel activity and increased receptor sensitivity.⁵⁸ The addition of nitrous oxide is more effective in reducing the requirements for potent inhaled anesthetic drugs in the elderly.

Undergoing surgery at an advanced age puts patients at increased risk for POD and postoperative cognitive dysfunction (POCD). Each of these entities is a strong risk factor for mortality.⁵⁹ The POD is a syndrome of fluctuating consciousness, inattention, memory impairment, and perceptual abnormalities that typically occurs after a lucid interval of 1 to 3 days after emergence from general anesthesia. The POCD is more loosely defined as a new, temporary decline in cognitive function (memory and executive function) manifesting 1 to 12 months after surgery and potentially lasting 2 to 3 years. A landmark study, the International Study of Postoperative Cognitive Dysfunction 1 described POCD in 26% of elderly patients 1 week after anesthesia and in 10% after 3 months using a variety of well-recognized neurocognitive assessments.⁶⁰ Subsequent studies have demonstrated incidence of POCD as 47% at 1 month, 23% at 2 months, and 15% at 6 months after surgery and anesthesia.⁶¹

The relationship between POD and POCD is unclear. There are a large number of shared risk factors, including advanced age, extent of surgery and duration of anesthesia, infection, and preexisting dementia or

cognitive decline.⁶² This suggests a shared pathogenesis. However, recent data from the Successful Aging after Elective Surgery trial did not show a correlation between POD and POCD beyond 1 month after surgery, suggesting that they may be distinct entities.⁶¹

A POD is equally common after both regional and general anesthesia, whereas POCD may be more common after general anesthesia.⁶³ A recent Cochrane review compared intravenous versus inhalational maintenance anesthetic for elderly patients undergoing noncardiac surgery. They could not make a conclusion about rates of POD between the two methods but found low-certainty evidence that POCD may be reduced with a propofol-based intravenous anesthetic.⁶⁴ Whereas some studies suggest a lighter depth of anesthesia is associated with decreased POD, other studies have not found this association.^{62,65,66} Despite this lack of consensus, the American Geriatric Society Expert Panel on Postoperative Delirium in Older Adults recommends the use of processed electroencephalography to maintain a lighter plane of anesthesia in an attempt decrease the incidence of POD.⁶²

The pathophysiology of acute POD in the elderly is undetermined. However, a neuroinflammatory response exacerbated by a faulty blood–brain barrier is thought to be mechanistically important. Surgical trauma induces a systemic inflammatory response, which leads to an inflammatory cascade mediated by neutrophils and macrophages in the central nervous system, which release cytokines, leukotrienes, free oxygen radicals, and proteolytic enzymes, damaging surrounding tissues and resulting in POCD. Other factors such as hypercapnia, hypotension, and cerebral microemboli have been areas of active investigation.⁶⁷

Although POCD is a risk factor for early mortality, in an 11-year follow-up of the International Study of Postoperative Cognitive Dysfunction cohort, it was not found to be a risk factor for dementia.⁶⁸ As the population ages and requires more surgical intervention, the pathogenesis of this syndrome and its best management are important areas for investigation.

Pain and Aging

Pain is a part of daily life for many elderly patients. In a large population-based study, 53% of older adults report “bothersome pain” in the last month. The prevalence of pain is increased in women, obese patients, and patients with multiple comorbid conditions.⁶⁹ Biologic, psychological, and social changes occur in the elderly that impact on the pain experience. The complexities of the pain response in the elderly are beyond the scope of this chapter, but clearly, aging is associated with changes in all three mentioned earlier.

In the simplest setting, experimental studies in healthy volunteers show that older adults are more sensitive than young adults to mechanically evoked pain but not heat-evoked pain.^{70,71} Descending inhibitory pathways, which function as an endogenous analgesic response to pain, are reduced in elderly patients. The number, density, and proportion of undamaged myelinated and unmyelinated nociceptive fibers decrease with age. Older individuals are more responsive to placebo interventions, which can be beneficial when used with appropriate informed consent.⁷²

As a general rule, elderly patients are more sensitive to opioids. Electroencephalographic, pharmacokinetic, and pharmacodynamic studies of subjects treated with fentanyl, alfentanil, sufentanil, and remifentanil support a 50% dose reduction for elderly patients.^{73–77} Aging results in less important pharmacokinetic effects of these drugs with variable reports of small reductions in clearance. Alterations in pharmacodynamics are more likely to be responsible for the observed dose reduction. It is important to remember that these drugs do not have active metabolites.

In contrast, morphine and meperidine do have active metabolites, which accumulate in the elderly. Morphine is altered by glucuronidation into two metabolites, morphine-3-glucuronide, which is mostly inactive, and morphine-6-glucuronide, which is itself a potent analgesic. Although the potency of intrathecal morphine-6-glucuronide is 650-fold higher than that of morphine, morphine-6-glucuronide crosses the blood–brain barrier so slowly that it is unlikely that it contributes to the acute analgesia provided by morphine. However, with chronic administration, the levels of morphine-6-glucuronide will rise to pharmacologically active concentrations.⁷⁸ Morphine-6-glucuronide is eliminated by the kidneys. Creatinine clearance is reduced with advancing age. Thus, morphine-6-glucuronide will accumulate more in elderly patients,

necessitating a reduction in dose of chronically administered morphine. Of course, in a patient with renal insufficiency, an opioid without a renally excreted active metabolite is a more appropriate choice.

Elderly patients have reduced meperidine clearance, resulting in a prolonged half-life. Meperidine will also accumulate in elderly subjects with repeated administration.⁷⁹ A toxic metabolite, normeperidine, is highly epileptogenic. Renal excretion of normeperidine is particularly reduced in elderly patients. The result is that normeperidine can accumulate with repeated doses in elderly patients.⁸⁰ This has resulted in several major healthcare policy organizations to state that meperidine is inappropriate for use in the elderly.⁸¹

Conclusion

The alterations in physiology and pharmacology discussed in this chapter encompass every organ system and result in overall decreased physiologic reserve, increased interindividual variability, and significant alterations in drug metabolism. This makes the anesthetic management of elderly patients more challenging. The continued aging of the population means that more and more elderly patients will require surgery, making anticipation and management of these factors critical. With careful drug titration and pre- and postoperative management, even the extremely old can safely undergo surgery in order to improve the quality of their lives.

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Physiology and Pharmacology of Resuscitation

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The term *resuscitation* for many people means resuscitation from cardiac arrest, so much so that the term *cardiopulmonary resuscitation (CPR)* is widely used not only by healthcare professionals but by lay people as well. This is justifiably so because cardiovascular disease is the number 1 cause of death in the United States, and in 2017, it is estimated that 647,457 Americans died of cardiovascular disease.^{1,2} Unfortunately, the first manifestation of cardiovascular disease is often sudden death due to ventricular tachycardia, ventricular fibrillation, or asystole. To improve outcome from cardiac arrest, the American College of Cardiology, American Heart Association, and many other organizations have joined together to educate healthcare professionals and lay people on how to resuscitate patients who have had a cardiac arrest by promoting the American Heart Association's Basic Life Support (BLS) and Advanced Cardiovascular Life Support (ACLS) programs. To incorporate the latest information on CPR, the programs are continuously updated.³

Resuscitation could equally apply to resuscitation from traumatic injury. Death from traumatic injury is the third leading cause of death overall in the United States and the primary cause of death in individuals younger the age of 45 years.⁴ These individuals most often die because of hemorrhage, and similar to what the American Heart Association has done, the American College of Surgeons through its Committee on Trauma has developed the Advanced Trauma Life Support course for healthcare professionals⁵ and the "Stop the Bleed"⁶ programs for the lay public to improve the outcome of patients who have sustained traumatic injury.

For a pediatrician, the mention of resuscitation might bring to mind the resuscitation of neonates with apnea.⁷ However, apnea or respiratory arrest is equally important in the resuscitation of adults from respiratory arrest, as it is distinct from cardiac arrest. If either is not recognized in a timely manner and treated effectively, then one will quickly precipitate the other.

Common to all these scenarios and the actual mechanism by which patients die is inadequate oxygen delivery to tissues. Oxygen delivery is defined as follows:

$$\dot{D}O_2 = CO \times CaO_2$$

where $\dot{D}O_2$ is equal to oxygen delivery, CO represents cardiac output, and CaO_2 is the oxygen content of arterial blood. In a 70-kg person, oxygen delivery is assumed to be 1000 mL per minute derived by multiplying cardiac output (50 dL per minute) times arterial oxygen content (20 mL of oxygen/dL), which in turn is calculated by multiplying 15 g hemoglobin/dL times 1.39 (the amount of oxygen each gram of hemoglobin can hold when fully saturated) times the arterial oxygen saturation (for this calculation, we are assuming a hemoglobin oxygen saturation of 100%). From this equation, one can gain insight into the three mechanisms from which death might occur if the patient is not resuscitated in a timely and effective fashion. During ventricular tachycardia, ventricular fibrillation, or asystole, cardiac output decreases to zero, as will oxygen delivery. During hemorrhagic shock, as hemoglobin levels decrease, the arterial oxygen content decreases at the same time that cardiac output falls because of decreased intravascular volume, resulting in decreased left ventricular end diastolic volume. During apnea from whatever cause, as whatever oxygen is contained in the functional residual capacity (FRC) of the lung decreases, the amount of oxygen available to bind with hemoglobin decreases, which also results in a steadily decreasing oxygen delivery and eventually cell death.

For the purposes of this chapter, the focus is on resuscitation from cardiac events, traumatic injury, and decreased fractional inspired concentration of oxygen (FIO_2).

Pathophysiology

The basic physiology of death from hypoxia due to decreased oxygen delivery is relatively straightforward but, at the same time, quite complex. As oxygenated hemoglobin is delivered to peripheral tissues, oxygen dissociates from hemoglobin because of the concentration gradient between the oxygenated hemoglobin in red blood cells and the decreased PaO_2 in capillary blood perfusing tissue. The dissociation of oxygen from hemoglobin is facilitated by the Bohr effect. Carbon dioxide that is produced by cellular respiration is released into capillary blood, combining with water to produce carbonic acid, which quickly dissociates into bicarbonate and hydrogen ion. The increased concentration of hydrogen ions results in a relative acidosis, which promotes the dissociation of oxygen from hemoglobin (shift of the oxygen-hemoglobin dissociation curve to the right). As oxygen dissociates from hemoglobin, it diffuses out of red blood cells and down a concentration gradient through the plasma, across cell membranes and into the cytoplasm where it is taken up by mitochondria, which in turn use the oxygen to catabolize pyruvate, derived from glucose, amino acids and fatty acids, in the Krebs cycle. Water and carbon dioxide are the byproducts, and the energy produced is used by the coenzymes nicotinamide adenine dinucleotide and flavin adenine dinucleotide to add a phosphate molecule to adenosine diphosphate to create adenosine triphosphate (ATP). The energy stored in the third phosphate bond of ATP can be used by cells for protein synthesis, for endocytosis and exocytosis, to provide energy for other transporter processes, for maintenance of the electrical potential across the membrane, and indeed to maintain the integrity of the cell membrane itself.

Oxygen is the molecule that serves as the electron acceptor by which nicotinamide adenine dinucleotide and flavin adenine dinucleotide produce more ATP than can be created by anaerobic metabolism. The chemical reactions involved in the anaerobic metabolism of pyruvate lead to the production of 4 molecules of ATP, whereas the metabolism of pyruvate in the presence of oxygen can lead to potentially 38 molecules of ATP. Anaerobic metabolism is insufficient in the long term to produce sufficient ATP to maintain cell integrity. In the absence of oxygen, cells die at a variable rate depending on their metabolic rate ([Figure 47.1](#)). Typically, neurons are the most sensitive to lack of oxygen and will develop irreversible damage within 3 to 5 minutes; myocytes and hepatocytes on the other hand can survive 1 to 2 hours in the absence of oxygen, whereas muscle cells may survive for several hours. By decreasing metabolic rate, hypothermia can prolong the “safe” ischemic time. Neurons, for example, decrease their metabolic rate by approximately 7% for every 1°C decrease in temperature.⁸ There is a limit, however, to how much hypothermia can delay a cell’s demise. For example, during circulatory arrest while a patient is on cardiopulmonary bypass, at 15°C to 20°C neurons do not display irreversible cell damage for as long as 30 to 40 minutes, but at 40 minutes, the risk for stroke and cognitive dysfunction increases significantly.⁹ Hypothermia has the same effect on other cells such as myocytes and hepatocytes as well as cells in other organs, which allow transplant surgeons to prolong the amount of time between when an organ is procured and when it is transplanted.

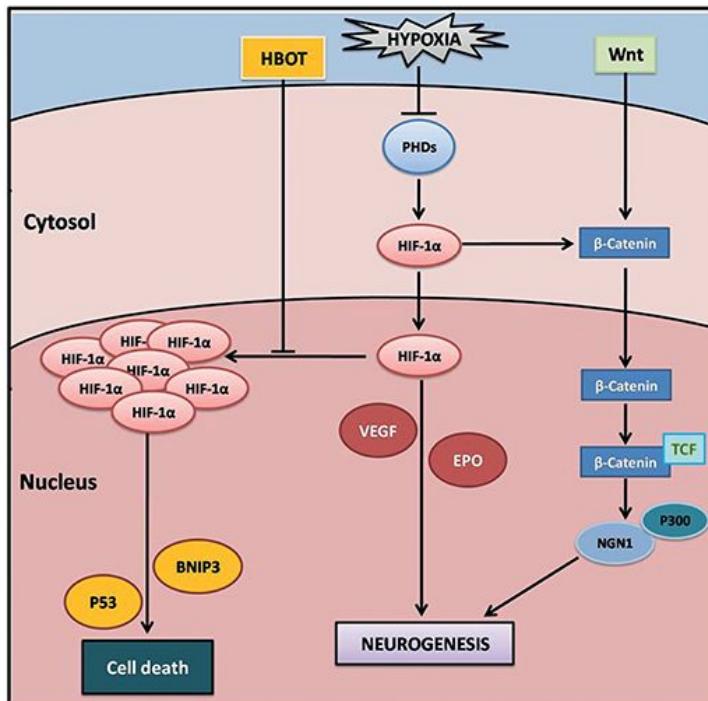


FIGURE 47.1 Physiologic pathways underlining hypoxic cellular responses in the brain. Abbreviations: BNIP3, BCL2/adenovirus E1B 19 kDa protein-interacting protein 3; EPO, erythropoietin; HBOT, hyperbaric oxygen therapy; HIF-1 α , hypoxia-inducible factor 1 alpha; NGN1, neurogenin 1; PHDs, prolyl hydroxylases; TCF, T-cell factor; VEGF, vascular endothelial growth factor.

Although temperature has an impact on survivability of ischemic cells, time is the factor that most directly and importantly impacts the reversibility of ischemia—the safe ischemic time. Independent of all other factors, the number of minutes that cardiac function is arrested, the amount of time that the hemoglobin concentration is below 6 to 7 g/dL, or the duration of apnea or asphyxia all directly correlate with morbidity and mortality. For cardiac arrest, evidence from assessment of the effect of duration of the arrest on survivability suggests that mortality increases by 8% to 10% for each minute for which there is no cardiac output.¹⁰ The most vital factor then in determining outcome is the timely restoration of normal cardiac, pulmonary, and hemodynamic function.

Cardiac Arrest

The National Library of Medicine in its Medical Subject Headings terms defines *heart arrest* as the cessation of effective cardiac function, which if not recognized and treated within minutes will lead to “sudden cardiac death” (SCD). The SCD in turn is the “unexpected rapid natural death due to cardiovascular collapse within one hour of the onset of symptoms usually caused by the worsening of existing heart disease.”

Thirty percent to 40% of patients who have an out-of-hospital cardiac arrest (OHCA) are found with ventricular tachycardia/ventricular fibrillation; ~20% of almost 12,000 patients admitted to central Massachusetts hospitals between 1986 and 2011 developed these same tachyarrhythmias.¹¹ Over a similar time frame though, the incidence of tachyarrhythmias has been decreasing.¹² Oftentimes, patients who have not had a myocardial ischemic event have a prolonged QT interval, which places them at increased risk for developing polymorphic ventricular tachycardia, for example, *torsade de pointes*, especially if they receive certain drugs that are also known to prolong the QT. Forty-seven mutations in genes that code for ion channels that generate the cardiac action potential have been identified in patients with the long QT syndrome.¹² More than 150 drugs have been reported to prolong the QT interval. Drugs that prolong the QT interval are thought to do so by modifying the activity of the same ion channels responsible for the long QT

syndrome. The effects of the different drugs range from mild to severe, with the latter having the greatest probability of precipitating *torsade de pointes*.¹³ The ability of a drug to precipitate a malignant tachyarrhythmia is related not just to the drug itself but also to the dose, drug-drug interactions, genetic factors, the sex of the patient, and the type and severity of preexisting cardiac disease.

The true incidence of the precipitating arrhythmia for an OHCA is not known because most sudden cardiac arrests occur out of hospital and typically several minutes pass before the rhythm can be assessed. The cardiac diseases that lead to the genesis of cardiac collapse are varied, and the association with SCD in some cases is not well understood. Similar to what has been found in some patients who have cardiovascular collapse from ventricular tachyarrhythmias, there are patients who develop ventricular fibrillation who do not have structural heart disease. One study identified inferolateral early repolarization in SCD patients who have no evidence of structural heart disease.¹⁴

For resuscitation to be successful, independent of the etiology of the cardiac collapse, CPR must be initiated as soon as possible. The best chance to improve outcome is the rapid return of spontaneous circulation (ROSC), which has led to a multiprong effort for OHCA.¹⁵ The foci have been on decreasing emergency medical services (EMS) response time, CPR training for the lay public, and increasing the number of automated external defibrillators in public places. Bystander initiation of BLS for a witnessed OHCA is associated with better outcomes than waiting for EMS to respond.¹⁶ The efficiency of BLS (eg, the quality of compressions) is critical,^{17,18} more so than ventilation.¹⁹ Next in the hierarchy is ACLS, supplied by EMS and emergency department personnel and by hospital personnel for in-hospital cardiac arrest. Once ROSC is achieved, more advanced technologies can be chosen, personalizing the resuscitation.¹⁵ Unfortunately, the average survival rate of OHCA of 7.6% did not change between 1980 and 2010.¹⁶ Predictors of increased survival for OHCA are EMS witnessed arrest, shockable rhythm, a cardiac as opposed to a noncardiac etiology, out-of-home versus in-home, and younger age.^{20,21} Better outcomes are also achieved if anesthesiologists are involved in prehospital care of patients, as they are in some European countries, who have sustained an OHCA.²²

For an arrest witnessed by a bystander trained in CPR, an EMS response time of ≤ 7.5 minutes is also associated with better outcomes.²³ For in-hospital cardiac arrest in those patients with a shockable rhythm, there is an inverse relationship between time to defibrillation and neurologic outcome; the goal should be to achieve defibrillation of ≤ 3 minutes.

Current ACLS guidelines deemphasize the importance of airway/breathing compared to return of circulation. The 2019 International Consensus on Cardiopulmonary Resuscitation suggested that bag-mask ventilation or ventilation through an advanced airway device be used during resuscitation from OHCA or in-hospital cardiac arrest, the choices depending on the skill of the personnel managing the airway. If a supraglottic device is used (in situations in which there is a low rate of success for tracheal intubation), no recommendations were made regarding the type of device that should be used.²⁴ Following ROSC, most patients will require tracheal intubation and mechanical ventilation.

For those patients with ROSC who are unresponsive, neurologic outcome is improved if hypothermia is induced for 24 hours. The 2015 guidelines of the International Liaison Committee on Resuscitation recommend targeted temperature management with a goal of 32°C to 36°C for patients with coma after ROSC from cardiac arrest.²⁵ A study from France published in 2019 demonstrated that patients in coma following ROSC after a cardiac arrest had improved neurologic outcome if targeted temperature management with a goal of 33°C was instituted for 24 hours.²⁶

Hemorrhagic Shock

In patients who sustain traumatic injury and die, hemorrhage accounts for the majority of deaths, oftentimes before patients arrive at a hospital. The same is true in combat where 67% of potentially preventable deaths are from hemorrhage. For those service members who were alive upon arrival at a combat support hospital in Afghanistan, severity of injury and hemorrhagic shock requiring a massive transfusion were significantly associated with mortality.²⁷

In both the civilian and military setting, mortality in the first several hours is also correlated with inadequate resuscitation²⁸ and the presence of coagulopathy.²⁹ A cascade of life-threatening conditions begins with severe hemorrhage, and many of these occur simultaneously creating a vicious cycle: (1) hemorrhage, (2) shock, (3) coagulopathy, (4) hypothermia, (5) hemorrhage. The goal for the anesthesiologist is to assess for and manage these problems simultaneously. Improvements in early hemorrhage control (damage control surgery³⁰), resuscitation, and the prevention and aggressive treatment of coagulopathy (damage control resuscitation³¹) appear to have the greatest potential to improve outcomes in severely injured trauma patients.

Pulmonary Arrest

Respiratory and cardiac arrest are distinct, but if untreated, one inevitably leads to the other. There are a multitude of etiologies of respiratory arrest, and respiratory arrest per se implies any process that inhibits the delivery of sufficient oxygen to the mitochondria to maintain aerobic metabolism. The respiratory centers are in the brainstem; they can be injured by penetrating injury (eg, a gunshot wound) or by increased intracranial pressure due to infection or an intraventricular hemorrhage. Even blunt trauma to the head of sufficient force can produce a similar result. Atkinson et al,³² using a mechanical blow to the head, demonstrated in a rodent model that as the force of the blow incrementally increased there came a point that the animal became completely apneic. A number of drugs can depress the respiratory centers, most notably the opioids, the sedatives, and the hypnotics (propofol, etomidate). These drugs can suppress ventilation or induce complete apnea even at low doses in patients with central sleep apnea^{33,34} or patients with chronic obstructive pulmonary disease (COPD) and hypercarbia, or in geriatric patients with comorbid conditions. Although it is true that opioids suppress ventilation, some have used this relationship to justify withholding opioids from patients with severe COPD at the end of their lives.³⁵ One study of over 2000 patients with severe COPD found a correlation between the dose of opioids and mortality, but at lower doses, the effect was not seen, and yet, lower doses did attenuate some of the patients' dyspnea.³⁶ More recent studies suggest that opioids continue to be used off-label to treat dyspnea in patients with COPD.^{37,38}

Whatever the cause, be it through a central nervous system mechanism or a peripheral mechanism such as glottic edema from anaphylactic shock or airway disruption from trauma or airway obstruction from a foreign body (eg, a piece of steak), death does not occur immediately. The hemoglobin in the circulating blood carries enough oxygen for maintenance of aerobic metabolism for 1 to 3 minutes. In addition, there is oxygen that has already entered the lungs. During normal breathing at end expiration, there is oxygen in the FRC that can be calculated as the FIO_2 times the volume of air in the FRC, which in turn is equal to the person's weight in kg times 15 mL/kg. For a 70-kg person breathing room air, the FRC would contain ~220 mL of oxygen ($[70 \text{ kg} \times 15 \text{ mL/kg}] \times 0.21$) enough to meet metabolic demand. At 3 to 4 minutes of complete apnea, evidence of tissue ischemia would become apparent, and, at >5 minutes, irreversible damage would occur, especially in the brain. Cardiac arrest would soon follow unless oxygenation and ventilation are immediately rapidly restored.

Other causes of hypoxic death are related to the neuromuscular system. A spinal cord transection above C4 would result in apnea that, if not recognized and treated, immediately will result in death simply because the phrenic nerves arise from C1 to C4. Likewise, in patients with amyotrophic lateral sclerosis, upper and lower motor neurons in the motor cortex, in the brainstem, and in the spinal cord self-destruct over time, leaving the patient unable to maintain respiratory effort. Neuromuscular blocking agents produce the same effect albeit more quickly.

Any process that increases the alveolar-to-arterial oxygen gradient can likewise interfere with the delivery of oxygen to tissues (eg, drowning) or acute respiratory distress syndrome.

Cyanide poisoning is the most well-known cause of inhibition of oxygen utilization within mitochondria by inhibiting of cytochrome c oxidase.

Using an alkaloid plant extract (curare) in which they dipped their arrows, the natives of Central and South America once killed their enemies.

All the causes of hypoxic death discussed so far come about from inhibition or destruction of the body's normal physiologic mechanisms. There are also environmental factors that play a role as well, the most important of which would be any factor that decreases the FIO_2 would interrupt aerobic metabolism. The best example for anesthesiologists would be a helium quench from a magnetic resonance imaging scanner that, if the proper safety valves in the room were not working correctly, would displace all the oxygen in the room.

Pharmacology

Cardiopulmonary Resuscitation

The primary goal when resuscitating a patient from cardiac arrest is ROSC, which is best achieved with effective chest compressions, and if the patient has a tachyarrhythmia, the delivery of electroshock therapy, as described in the preceding text. However, if these maneuvers are unsuccessful in restoring cardiac function, drug therapy is advocated because it has been shown to increase the rate of ROSC. Amiodarone, lidocaine, and epinephrine are three such drugs; vasopressin, sodium bicarbonate, fibrinolytics, and other vasoactive drugs have not been shown to increase the rate of ROSC and therefore their use is no longer advocated.

Epinephrine

Epinephrine is a catecholamine (vasoactive compound with a catechol—benzene ring with two hydroxyl groups [[Figure 47.2](#)] in its structure) for which dopamine is its precursor, and in turn epinephrine is the precursor for norepinephrine. Chromaffin cells in the adrenal medulla and the terminal boutons of certain nerves produce and release epinephrine, which gains its biologic activity by binding to α - and β -adrenergic receptors. Among its many effects, epinephrine activation of α -receptors produces vasoconstriction in the peripheral vasculature, whereas activation of β -receptors within the heart increases chronotropy, inotropy, dromotropy, and lusitropy. The majority of epinephrine produced is metabolized within the same cells in which it was synthesized simply because there is so much leakage of the catecholamine from the vesicles where it is stored in the cytoplasm.

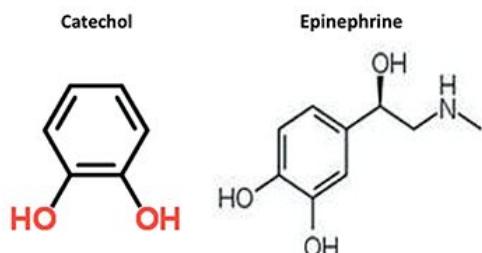


FIGURE 47.2 Molecular structure for the common catechol ring and for epinephrine.

When administered intravenously during a cardiac arrest, epinephrine is thought to increase the ROSC by binding to and activating α -adrenergic receptors. Activation of these receptors on the venules in the periphery would increase venous return to the heart and during chest compressions would increase cardiac output; on the arterial side, the vasoconstriction caused by α -receptor activation would constrict the peripheral arterial system. The increase in cardiac output with an increased systemic vascular resistance is hypothesized to improve coronary artery and carotid artery blood flow. By activating β -receptors within the heart, epinephrine should augment cardiac output even further, with additional benefit to the patient, but there are some who believe that epinephrine's effect on β -receptors is more detrimental than beneficial.

Epinephrine has been repeatedly demonstrated to improve ROSC when administered to patients in cardiac arrest but without an improvement in overall outcome. However, most of the studies of epinephrine have been observational in nature; in 2012, the only prospective randomized controlled study ever done until that time was stopped early because of difficulty enrolling patients into the placebo group.³⁹ During the intervening years, questions continued to arise about the role of epinephrine in cardiac arrest.^{40,41} Perkins et

al⁴² studied 8014 patients with OHCA who were randomized to either epinephrine (n = 4015) or placebo (n = 3999). The primary end point was 30-day survival, and a secondary end point was neurologic status. Patients administered epinephrine had better 30-day survival rates (3.2%) than those who received placebo (2.4%). More patients in the former group (31%) had devastating neurologic outcome with Rankin scores of 4 to 5, compared to the latter group (17.8%). The difference in survival rates was not enough to compensate for the difference in neurologic status, and in fact, the reverse was true.⁴² Unless the American Heart Association guidelines are changed, it is recommended that clinicians follow ACLS protocols when resuscitating patients who sustain a cardiac arrest. They are well established and well accepted by the medical and lay public communities.⁴³ The study highlights the fact that although the administration of epinephrine during CPR may increase the likelihood of ROSC, it may not improve neurologic outcome, but the same is true for every other drug that has been studied when administered during CPR.⁴⁴ However, the most recent guidelines of the American Heart Association recommend 1 mg of epinephrine administered intravenously or by intraosseous (IO) injection every 3 to 5 minutes. If these routes are not available, epinephrine can be given through the tracheal tube if one is present. The optimal dose is unknown, but typically, 2 to 2.5 times the intravenous dose is recommended. The dose should be diluted in 5 to 10 mL of sterile water or saline for tracheal tube administration.

The 2019 International Consensus on Cardiopulmonary Resuscitation guidelines for resuscitation include the strong recommendation that epinephrine continue to be used during CPR. For nonshockable rhythms, epinephrine should be administered as soon as possible. For shockable rhythms, epinephrine should be administered if ROSC is not achieved with initial defibrillation. The authors of the guidelines placed a great deal of credence in the potentially life-saving benefit of ROSC when epinephrine is administered during CPR. They acknowledge the downside of perhaps worse long-term neurologic outcomes and the cost to society of poor functional status. However, the latter should serve as a stimulus for studies to improve not just survivability but functional status as well.²⁴

Based on several studies, the most recent of which are several years old,⁴⁵ the guidelines continue to recommend against the administration of vasopressin for CPR protocols.²⁴

Amiodarone

Electric defibrillation is first-line treatment for ventricular fibrillation. Amiodarone is second-line pharmacologic treatment (after epinephrine) or in patients who have ventricular fibrillation refractory to electric defibrillation. Administered intravenously at a dose of 300 mg⁴⁶ or 5 mg/kg⁴⁷ amiodarone compared to lidocaine has been shown to be superior for ROSC in patients with ventricular fibrillation refractory to electric defibrillation. However, no study has yet demonstrated that long-term outcome in terms of morbidity or mortality is improved. However, the American Heart Association has recommended amiodarone to treat refractory ventricular fibrillation or pulseless ventricular tachycardia.⁴⁸

Following intravenous administration of amiodarone, it enters a central compartment, and from there, it undergoes extensive tissue redistribution. The distribution half-life of amiodarone out of the central compartment to these other tissues ($t_{1/2\alpha}$) may be as short as 4 hours. The terminal half-life ($t_{1/2\beta}$) is lengthy and also variable (9-77 days) because of prolonged release of amiodarone out of adipocytes due to the lipophilicity of the drug.^{49,50}

Hemodynamic effects of orally administered amiodarone are usually negligible; administered intravenously, there have been reports of hypotension, but the hypotension seen with intravenous amiodarone in the past was thought due to the vasoactive solvents (polysorbate and benzyl alcohol) in which it was compounded. When administered with a different diluent, rapid administration of amiodarone intravenously is not associated with hypotension.⁵¹ In terms of route administration, the intravenous administration of amiodarone may be preferable compared to the IO route. In one recent study of OHCA, survival to hospital admission was significantly better if either amiodarone or lidocaine was administered intravenously compared to IO, and more patients survived to hospital discharge when drugs were given IV compared to IO with slightly better neurologic outcome.⁵²

Effects of amiodarone on the thyroid gland and the liver are significant.^{53,54} The similarity between the chemical structures of amiodarone and thyroid hormone explain the former, and the latter is most likely due to direct injury to lipid bilayers of the hepatocyte cell membrane and inhibition of lysosomal function.⁵⁵ However, these adverse effects are seen in patients taking the drug in high doses for extended periods of time but not in patients who are administered one or two doses of the drug during sudden cardiac arrest.

Lidocaine may be considered as an alternative to amiodarone for ventricular fibrillation/pulseless ventricular tachycardia that is unresponsive to CPR and defibrillation.⁵⁶ A study published after the 2015 ACLS protocols were updated confirmed that neither lidocaine nor amiodarone significantly improved survival compared to placebo for OHCA, but there were subgroups of patients (eg, witnessed arrest) in whom outcomes were better if either drug was administered. Interestingly, patients who were administered amiodarone were more likely to require temporary pacing compared to those who received lidocaine or placebo.⁵⁷

Hemorrhage

The most critical intervention for someone who is bleeding is to stop the bleeding—either by applying a tourniquet to an extremity in the field or, if there is massive internal bleeding from a crush injury or ruptured aortic aneurysm, by transporting the patient as quickly as possible to a level I trauma hospital and from the emergency department to the operating room. The importance of surgical intervention as quickly as possible was underscored by Mattox and colleagues in a study of patients who were transported by emergency medical personnel and who were randomized to what at the time was conventional therapy of placing an intravenous cannula and initiating the infusion of crystalloid during transport to the hospital or to essentially no therapy, the “scoop and run” approach: emergency personnel evaluated the patient; treated the airway, breathing, and circulation; and then placed the patient in the ambulance with immediate transport back to the hospital. The latter group not only received less crystalloid but also had better survival than the conventionally treated group.⁵⁸

Other components of damage control resuscitation include maintaining normal temperature and pH, limiting intravenous crystalloid to maintain euvolemia, using a hemoglobin target of 7 to 8 g/dL to allow appropriate tissue oxygen delivery, and identifying patients at risk for developing acute traumatic coagulopathy. Multiple clinical studies have shown a benefit of a 1:1:1 ratio of packed red blood cells and the transfusion of platelets and fresh frozen plasma in severely injured and rapidly bleeding patients, as part of the damage control resuscitation. There are ongoing initiatives to determine if other practices can improve outcome in patients who sustain severe traumatic injury and develop acute coagulopathy of trauma.^{31,59} Prehospital administration of thawed plasma as the primary resuscitation fluid in one study demonstrated a lower 30-day mortality and lower median prothrombin time ratio than standard care resuscitation.⁶⁰ Of more importance though is the increasing use of whole blood in the prehospital⁶¹ and intrahospital⁶² management of trauma patients. In academic centers where whole blood is being transfused, either low titer O Rh-positive or O-negative blood is used simply because of the shortage of blood.⁶³

Tranexamic Acid

As with resuscitation from cardiac arrest, there is a limited role for drugs in improving outcome in patients who sustained traumatic injury with possibly one exception. In the CRASH-2 trial, such patients were randomized to a tranexamic acid group or control to examine the impact on death, vascular occlusive events, and transfusion requirement.⁶⁴ The group that was administered tranexamic acid early had a small but reduced risk of death (1.6% in all comers—a recent subgroup analysis suggested a 2.5% reduction) and was cost-effective, especially when given within an hour of admission. Beyond 3 hours, there appeared to be an increase in mortality. There has also been interest in using recombinant human factor VIIa and prothrombin complex concentrate in some trauma centers for coagulopathy, sometimes as salvage therapy. Further studies are necessary to determine the appropriate and effective utilization of these adjunct treatments.

Tranexamic acid, a synthetic analogue of the amino acid lysine (**Figure 47.3**), is an antifibrinolytic that has found widespread use following the removal of aprotinin from the market. By binding to specific sites on

plasminogen and plasmin, it inhibits the transformation of plasminogen to plasmin. Circulating plasmin degrades fibrin, an integral part of blood clots. Tranexamic acid's role in managing patients with traumatic injury has not yet been determined, but there are a number of level 1 trauma centers in the United States, that administer it routinely to their patients.

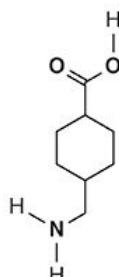


FIGURE 47.3 Molecular structure for tranexamic acid.

Oxygenation/Ventilation

As with patients with cardiac arrest in whom defibrillation in the first 3 minutes and CPR/defibrillation during the next 5 to 7 minutes achieves the best results, and as with patients with profound hemorrhage in whom immediate control of the bleeding and infusion of blood product has the biggest impact on outcome, for patients with pulmonary or respiratory arrest, immediate-assisted ventilation and oxygenation is the most likely intervention to increase the chances of survival. No drugs have been demonstrated in large prospective randomized trials to improve the chances of successful resuscitation. For pulmonary arrest, there are some exceptions (eg, for some causes of pulmonary arrest secondary to an opioid or less likely a benzodiazepine overdose), as the administration of naloxone for the former and flumazenil for the latter will antagonize the effects of the respective receptor's agonist, with an excessive dose (intentional, unintentional, or iatrogenic).

Likewise, for patients with cyanide toxicity and respiratory arrest at the cellular level, hydroxocobalamin is an antidote for cyanide toxicity that is effective with a high benefit-to-risk ratio and therefore safe in acute cyanide poisoning. Amyl nitrite and sodium nitrite are also effective because they promote the conversion of hemoglobin and cyanide ions to methemoglobin. Nitrites are not suitable for fire victims and those with poor cardiopulmonary reserve. Sodium thiosulfate is a sulfur donor; thiosulfate-cyanide transferase (rhodanese) converts cyanide ion to the less toxic thiocyanate.⁶⁵ These drugs are discussed elsewhere ([Chapter 20](#)).

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Note: Page numbers followed by *f* indicate figures; page numbers followed by *t* indicate tables.

A

- Abciximab, 669–670
Acarbose, 777
Acbutolol, 475*f*, 476*t*, 485, 502, 517*t*, 527
Acetaminophen (Tylenol, Paracetamol), 262–263, 913
Acetazolamide, 535–536
Acetohexamide, 773*t*, 774*f*
Acetylsalicylic acid (Aspirin), 259*f*, 261*t*, 263–264, 668, 669, 669*t*, 896*t*
Acrivastine, 719*t*, 720
Acylaminopenicillins, 815
Adenosine, 513, 520*t*, 532
Albuterol (salbutamol), 80*t*, 460*f*, 460*t*, 461, 596, 596*t*, 597
Alcohols, 821–822
Aldosterone, 265*t*, 484, 784*f*, 784*t*
Alemtuzumab, 834*t*, 848
Alendronate, 791
Alfentanil, 30*f*, 32–33, 33*f*, 34*f*, 35*t*, 37*f*, 39*f*, 40*f*, 42*f*, 45, 89, 124, 154, 207*f*, 207*t*, 215*t*, 221*f*, 224–225, 897*t*
Alfuzosin, 473
Alirocumab, 548
Alkylating agents, 829*t*, 830*t*–831*t*, 836–839
Alkyl sulfonates, 830*t*, 838
Almitrine, 356
Alogliptin, 773*t*, 777
Alprazolam, 163
Aluminum hydroxide, 718, 726
Alvimopan, 233, 233*f*
Amantadine, 353
Ambien. *See* Zolpidem
Amethocaine, 290
Amikacin, 818
Amiloride, 541
Aminoglutethimide, 829*t*, 835*t*
Aminoglycoside, 805*t*–809*t*, 811*t*, 813*t*, 817–818
Aminophylline, 598*t*, 600, 880*t*
Amiodarone, 517*t*, 519, 519*t*, 520*t*, 528–530, 528*f*, 529*f*, 940–941
Amisulpride, 709*t*, 713, 870*t*, 875
Amitriptyline, 856*t*, 861, 864
Amlodipine, 487*t*, 493, 506
Amoxapine, 856*t*
Amoxicillin, 815, 902*t*
AMPA, 57
Amphetamine, 80*t*
Amphotericin B, 811*t*
Ampicillin, 803*t*, 808*t*, 815, 902*t*
Ampicillin-sulbactam, 803*t*, 805*t*–809*t*, 810
Ampyrone, 259*f*

Amrinone (Inamrinone), 465*f*, 507
Anastrazole, 829*t*, 835*t*
Andexanet, 668
Androgens, 762–763, 797–798, 797*f*, 798*f*, 847
Anthracenediones, 832*t*
Anthracyclines, 829*t*, 832*t*
Antiandrogens, 829*t*, 834*t*, 847
Antidiuretic hormone (ADH), 53*t*, 369
Antiestrogens, 796, 796*f*, 829*t*, 834*t*, 847
Antimetabolites, 829*t*, 831*t*–832*t*, 840–842
Antiprogestins, 796, 797*f*
Antitumor antibiotics, 829*t*, 833*t*
Apixaban (Eliquis), 661*f*, 665*t*, 667, 668
Aprepitant, 709*t*
Aprotinin, 652
Arformoterol, 596*t*
Argatroban, 661, 661*f*, 664, 664*t*, 896*t*
Aripiprazole, 870*t*, 874–875
Armodafinil, 869
Aromatase inhibitors, 829*t*, 835*t*, 847–848
Aspirin. *See* Acetylsalicylic acid
Atenolol, 453*f*, 475*f*, 476*t*, 479, 483, 485, 502, 895*t*
Atezolizumab, 849, 850*t*
Atipamezole, 184
Atomoxetine, 867
Atorvastatin, 547
Atracurium, 45, 315*t*, 318, 900*t*
Atropine, 80*t*, 161, 178, 322, 464, 482, 596*t*, 597, 709*t*, 711
Avitene, 656
Azelastine, 719*t*
Azithromycin, 819, 902*t*
Azlocillin, 815
Azosemide, 536, 538
Aztreonam, 803*t*, 805*t*–809*t*, 817

B

Bacitracins, 820
Baclofen, 251, 356
Barbiturates, 23, 46, 172–176
Bebulin VH, 656
Beclomethasone, 598*t*
Benserazide, 352
Benzalkonium, 823
Benzocaine, 280, 289*t*
Benzodiazepines, 57, 62, 69, 161–172, 162*f*, 285, 342, 343, 348–349, 357, 878
Benztropine, 353, 869
Betamethasone, 265*t*, 784*t*, 785, 785*f*
Betaxolol, 475*f*, 476*t*, 479
 β -Lactams, 811*t*, 815–817
Bevacizumab, 834*t*, 848

Bezafibrate, 549
Bicalutamide, 829*t*, 834*t*, 847
BioGlue, 656
Bisoprolol, 477*t*, 479, 485, 486, 502
Bisphosphonates, 442–443, 443*f*, 791
Bivalirudin, 661, 661*f*, 663, 664*t*
Bleomycin, 829*t*, 833*t*, 844–845, 844*f*, 845*t*
Botulinum toxin, 80*t*, 357
Bremazocine, 207*t*, 230
Bretazenil, 13*f*, 14–15, 41
Bretylium, 80*t*
Brexpiprazole, 874–875
Bromocriptine, 352, 777
Brompheniramine, 720*f*
Budesonide, 598*t*
Bumetanide, 512, 536, 538
Bupivacaine, 44, 45, 273, 273*f*, 274*t*, 277–279, 281–286, 284*f*, 288*t*, 291–293, 291*t*, 292*f*, 294*f*, 296, 296*f*, 478, 608, 726, 727*f*, 901*t*, 913
Buprenorphine, 207*t*, 230*f*, 231, 897*t*
Bupropion, 868
Buserelin, 829*t*, 835*t*, 847–848
Buspirone, 856*t*, 860
Busulfan, 830*t*, 838
Butorphanol, 207*t*, 230*f*, 231
Butyrophenones, 713

C

Caffeine, 355, 356
Calcitonin, 759
Calcium carbonate, 718
Calcium chloride, 482
Camptothecins, 833*t*
Canagliflozin, 773*t*, 776
Candesartan, 506
Cangrelor, 668–669, 670*f*
Cannabis, 881
Capecitabine, 841
Capsaicin, 267
Captopril, 505, 506
Carbachol, 80*t*, 248*f*
Carbamazepine, 339*t*, 340*t*, 342*t*, 343–344, 876, 880*t*
Carbazalone, 709
Carbenicillin, 815
Carbidopa, 352
Carbimazole, 780–781
Carboplatin, 829*t*, 831*t*
Carboxypenicillins, 815
Carfentanil, 207*t*
Cariprazine, 874–875
Carmustine, 830*t*, 838–839

Carvedilol, 477*t*, 486, 487, 500, 502
Cefamandole, 809*t*
Cefazolin, 803*t*, 805*t*–808*t*, 810, 816–817, 902*t*
Cefepime, 817, 902*t*
Cefixime, 817
Cefotaxime, 803*t*, 808*t*, 817
Cefotetan, 803*t*, 805*t*–807*t*, 810
Cefoxitin, 803*t*, 805*t*–808*t*, 810, 817, 902*t*
Cefpirome, 817
Ceftaroline, 817
Ceftobiprole, 817
Ceftriaxone, 803*t*, 805*t*, 806*t*, 810, 817, 902*t*
Cefuroxime, 803*t*, 805*t*, 817
Celecoxib (Celebrex), 257–258, 259*f*, 261*t*
Cephalosporins, 811*t*, 813*t*, 815–817
Cephalexin, 816
Cetylpyridinium, 823
CGX-1160, 251
Chlorambucil, 829*t*, 830*t*, 838
Chloramphenicol, 811*t*, 813*t*
Chlorhexidine, 822
Chloroform, 95, 96*f*
Chloroprocaine, 272, 273*f*, 274*t*, 279–281, 288*t*, 289, 292, 294*f*, 901*t*
Chlorpheniramine, 719*t*, 720, 720*f*
Chlorpromazine, 709*t*, 870, 870*t*
Chlorpropamide, 773*t*, 774*f*
Chlorthalidone, 539
Cholestyramine, 549
Choline magnesium, 261*t*
Ciclesonide, 598*t*
Cimetidine, 496, 722–723, 722*f*, 723*t*, 724–726, 725*t*, 726*f*, 727*f*
Ciprofloxacin, 803*t*, 821, 902*t*
Cisapride, 731
Cisatracurium, 45, 315*t*, 319, 603
Cisplatin, 829*t*, 831*t*, 839
Citalopram, 856*t*, 859
Cladribine, 832*t*, 842
Clavulanic acid, 815
Clevidipine, 487*t*, 492, 501*t*, 506–507, 508
Clindamycin, 803*t*, 805*t*–809*t*, 813*t*, 819, 902*t*
Clinoril. *See* Sulindac
Clobazam, 349
Clofibrate, 549
Clomiphene, 796, 796*f*
Clomipramine, 856*t*, 859–860, 864
Clonazepam, 340*t*, 342*t*, 348–349, 878
Clonidine, 25, 80*t*, 124, 184, 247, 248*f*, 267, 280, 473, 503–505, 867–868, 895*t*
Clopidogrel (Plavix), 495, 668, 669, 669*t*, 896*t*
Cloxacillin, 814
Clozapine, 870*t*, 873–874
Cocaine, 80*t*, 272, 273*f*, 280, 289, 289*t*, 297–298, 298*f*, 454

Codeine, 17, 45, 183, 207*f*, 207*t*, 228, 897
Colesevetam, 549, 777
Colestipol, 549
Cortisol, 265*t*, 541, 784–785, 784*f*, 784*t*
Cortisone, 265*t*, 784*f*, 784*t*
CoSeal, 656
Coxibs, 257–258, 261*t*
Cresol, 823
Cromolyn sodium, 598*t*, 599
Crosseal, 656
Cyclizine, 712
Cyclobenzaprine, 357
Cyclophosphamide, 829*t*, 830*t*, 837
Cyclopropane, 96*f*
Cyclosporine, 112
Cytarabine, 831*t*, 841

D

Dabigatran etexilate (Pradaxa), 661*f*, 664*t*, 666–668, 896*t*
Dacarbazine, 831*t*
Dactinomycin, 833*t*, 843–844
Dalteparin, 662, 663, 668
Danaparoid, 663, 665*t*
Danazol, 797*f*, 798
Dantrolene, 357
Dapagliflozin, 773*t*
Daratumumab, 835*t*, 848
Daunomycin, 832*t*
Daunorubicin, 842–843
Daypro. *See* Oxaprozin
DDAVP. *See* Desmopressin
Degludec, 771, 771*t*
Denosumab, 444
Desflurane, 42*f*, 89, 95, 96, 96*f*, 96*t*, 97*f*, 98, 104*t*, 108*f*, 109–110, 109*f*, 111*t*, 112*f*, 114, 116–122, 118*f*–122*f*, 124–127, 124*f*, 125*f*, 128*f*–133*f*, 128*t*, 129, 131, 133–134, 136–138, 137*f*, 140, 140*t*, 155, 221*f*, 483, 600, 606
Desipramine, 725*t*, 856*t*, 864
Desirudin, 663, 664, 664*t*
Desmethyldiazepam, 168–169, 168*f*
Desmopressin (DDAVP), 653–654, 793–794
Desvenlafaxine, 856*t*, 859
Detemir, 771, 771*t*
Dexamethasone, 264, 265*t*, 709, 709*t*, 712, 784*t*, 785–786
Dexmedetomidine, 39*f*, 184–185, 185*f*, 247–248, 267, 280, 473–474, 915
Dextran, 669
Dextroamphetamine, 868
Dextromethorphan, 183
Dextropropoxyphene, 527
Dezocine, 207*t*, 230
Diazepam, 17, 46, 162, 164, 165*t*, 168–170, 168*f*–170*f*, 170*t*, 171, 183, 285, 342*t*, 349, 726, 726*f*, 899*t*

Diazoxide, 513
Dibucaine, 279, 316, 316*t*
Diclofenac (Voltaren), 259*f*, 260*t*
Dicloxacillin, 814
Diethyl ether, 95
Diflunisal, 259*f*
Digitalis, 461, 494, 520*t*, 532
Digitoxin, 461, 462*f*
Digoxin, 461–464, 462*f*, 463*f*
Diltiazem, 487*t*–489*t*, 488*f*, 489, 491*f*, 493, 494, 506, 517*t*, 520, 520*t*, 531–532, 895*t*
Dimenhydrinate (Dramamine), 709*t*, 712, 721
Diphenhydramine, 709*t*, 712, 719*t*, 720*f*, 721
Dipyridamole, 669
Disopyramide, 517*t*, 518, 519*t*, 520*t*, 524, 524*f*
Divinyl ether, 96*f*
Dobutamine, 80*t*, 451*t*, 452, 452*f*, 457–458, 465–466
Docetaxel, 829*t*, 833*t*, 846
Dofetilide, 517*t*, 520, 531
Dolasetron, 709*t*, 710
Domperidone, 712, 713, 728–729, 729*f*
Donepezil, 877
Dopamine, 451*t*, 452*f*, 454–456, 542, 604, 609
Doxapram, 354, 355*f*
Doxazocin, 502
Doxazosin, 472–473
Doxepin, 856*t*, 861
Doxorubicin, 829*t*, 832*t*, 842–843, 843*f*
Dramamine. *See* Dimenhydrinate
Dronabinol, 709*t*, 714
Dronedarone, 517*t*, 519, 519*t*, 530
Droperidol, 250, 709, 709*t*, 712, 713
Duloxetine, 859
Durvalumab, 849, 850*t*
Dyclonine, 296

E

EACA. *See* Epsilon aminocaproic acid
Edoxaban (Savaysa), 661*f*, 667
Edrophonium, 80*t*, 248*f*, 322, 711
Effient. *See* Prasugrel
Empagliflozin, 773*t*, 776
Enalapril, 505, 506
Enalaprilat, 505, 506
Enflurane, 95, 96*f*, 96*t*, 98, 104*t*, 105, 105*f*, 110, 111*t*, 116, 117, 117*f*, 119, 121*f*, 123, 128*t*, 132*f*, 133–134, 133*f*, 137*f*, 139, 140, 140*t*, 606
Enoxaparin, 662, 663, 896*t*
Entacapone, 352
Ephedrine, 451*t*, 458, 458*f*, 750, 911
Epinephrine, 281, 281*f*, 285, 290–293, 294*f*, 297, 450–453, 451*t*, 452*f*, 453*f*, 454, 480, 486, 596*t*, 597, 604, 609, 721, 939–940, 939*f*

Epipodophyllotoxins, 832*t*–833*t*
Epirubicin, 829*t*, 832*t*
Eplerenone, 541–542
Epoprostenol, 605
Epsilon aminocaproic acid (EACA), 651–652
Eptifibatide, 670
Ertapenem, 803*t*, 806*t*, 810, 902*t*
Ertugliflozin, 773*t*
Erythromycin, 731, 731*f*, 804*t*, 811*t*–813*t*, 818–819
Erythromycin estolate, 813*t*
Escitalopram, 856*t*, 859
Esketamine, 176, 877
Eslicarbazepine, 339*t*, 340*t*, 342*t*, 344
Esmolol, 18, 80*t*, 124, 474, 475*f*, 476*t*, 480–481, 480*f*, 485, 501*t*, 517*t*, 527
Esomeprazole, 727*t*, 728
Estramustine, 846
Estrogen, 25
Estrogens, 763, 795–796, 795*f*, 847
Eszopiclone (Lunesta), 172, 878
Ethacrynic acid, 536–537
Ethambutol, 811*t*, 813*t*
Ether, 96*f*
Ethosuximide, 339*t*, 340*t*, 342*t*, 344
Ethyl alcohol, 821
Ethyl chloride, 96*f*
Ethylene, 96*f*
Ethyleneimine, 830*t*
Ethylene oxide, 824
Ethylestrenol, 797*f*
Ethyl vinyl ether, 96*f*
Etidocaine, 272–273, 273*f*
Etodolac (Lodine), 259*f*, 260*t*
Etomidate, 35*t*, 39*f*, 57, 70, 151*t*, 153*f*, 155, 158–161, 160*f*, 161*f*, 603, 899*t*
Etoposide, 829*t*, 832*t*
Evinel, 656
Evithrom, 656
Evolocumab, 548
Exemestane, 847
Exenatide, 776
Ezetimibe, 546*f*, 547*t*, 550

F

Factor XIII (Fibrogammin), 655
Famotidine, 722–724, 722*f*, 723*t*, 726
FEIBA, 656
Felbamate, 339*t*, 340*t*, 342*t*, 344
Feldene. *See* Piroxicam
Felodipine, 487*t*
Fenfluramine, 706
Fenofibrate, 549–550

Fenoldopam, 501*t*, 508, 512, 542
Fenoprofen (Nalfon), 259*f*, 260*t*
Fentanyl, 25, 30*f*, 32–33, 33*f*, 34*f*, 35*t*, 36*f*, 37*f*, 39*f*, 40, 40*f*, 42, 42*f*, 45, 46, 70, 113, 124, 129, 165, 166, 207*f*, 207*t*, 214*t*, 215*t*, 219–223, 220*f*–222*f*, 235*t*, 293, 478, 480, 603, 608, 897*t*
Fexofenadine, 720*f*, 721
Fibrinogen, 654
Fibrogammin. *See* Factor XIII
Finasteride, 798, 798*f*
Flecainide, 517*t*, 519, 519*t*, 520*t*, 526–527, 526*f*
FloSeal, 656
Fluconazole, 803*t*, 808*t*
Flucytosine, 811*t*
Fludarabine, 832*t*
Fludrocortisone, 265*t*, 784*t*, 785*f*
Flumazenil, 13*f*, 14–15, 41, 162, 166, 171–172
Flunisolide, 598*t*
Fluoroquinolones, 805*t*–809*t*, 812*t*, 813*t*, 820–821
Fluorouracil, 831*t*, 840–841
5-Fluorouracil, 829*t*
Fluoxetine, 856*t*, 859
Fluphenazine, 870, 870*t*
Flurbiprofen (Ocufen), 259*f*, 260*t*
Fluroxene, 96*f*
Flutamide, 829*t*, 834*t*, 847
Fluticasone, 598*t*
Fluvastatin, 547
Fluvoxamine, 856*t*, 859
Fondaparinux, 662–663, 665*t*, 896*t*, 905
Formaldehyde, 823
Formoterol, 596*t*
Fosaprepitant, 709*t*
Fulvestrant, 847
Furosemide, 512, 536–537, 880*t*, 895*t*

G

Gabapentin, 339*t*, 340*t*, 342*t*, 344, 876
Galantamine, 877–878
Gatifloxacin, 807*t*
Gelfoam, 656
Gemcitabine, 829*t*, 831*t*, 841
Gemfibrozil, 549–550
Gentamicin, 803*t*, 818, 902*t*
Glargine, 771, 771*t*
Gliclazide, 773*t*
Glimepiride, 773*t*, 774*f*, 775*t*
Glipizide, 773*t*, 774*f*, 775, 775*t*
Glulisine, 771, 771*t*
Glutaraldehyde, 823
Glyburide, 773*t*, 774*f*, 775, 775*t*
Glycerin, 540

Glycopyrrolate, 178, 322, 596*t*, 597, 711, 914
Goserelin, 847–848
Granisetron, 709*t*, 710
Guanfacine, 867

H

Haloflurane, 130*f*
Haloperidol, 709*t*, 713, 870, 870*t*
Halothane, 95, 96*f*, 96*t*, 97–98, 102*f*, 103*f*, 104*t*, 105, 105*f*, 108*f*, 111*t*, 114*f*, 116, 117*f*–122*f*, 118–123, 128, 128*f*, 128*t*, 129, 131, 132–133, 132*f*, 133*f*, 134, 136, 137, 137*f*, 138, 140, 140*t*, 600*t*, 606
Heliox, 602
Helium, 602
Heparin, 477, 477*f*, 660–662, 661*f*, 665*t*, 896*t*, 905, 914
Heroin, 207*t*, 214*t*, 230
Hexachlorophene, 823
Hexamethonium, 80*t*
Hexamethylmelamine, 830*t*
Hydralazine, 46, 501*t*, 512, 742, 895*t*
Hydrochlorothiazide, 539
Hydrocodone, 207*t*, 229, 897*t*
Hydromorphone, 39*f*, 207*t*, 229, 235*t*, 897*t*
Hydroxyprogesterone caproate, 797*f*
Hydroxyurea, 832*t*, 842
Hydroxyzine, 719*t*
Hyoscine, 709*t*

I

Ibuprofen (Motrin), 259*f*, 260*t*
Ibutilide, 517*t*, 531
Idarubicin, 832*t*
Ifosfamide, 829*t*
Iloperidone, 874
Iloprost, 605
Imatinib, 835*t*, 848
Imipramine, 725*t*, 856*t*, 859, 864
Inamrinone. *See* Amrinone
Indapamide, 539
Indocin. *See* Indomethacin
Indomethacin (Indocin), 259*f*, 260*t*
Insulin aspart, 771, 771*t*
Iodine, 781, 822
Iodophors, 822
Ipilimumab, 849, 850*t*
Ipratropium, 596*t*, 597
Irbesartan, 506
Irinotecan, 829*t*, 833*t*
Isocarboxazid, 856*t*, 861
Isoflurane, 42*f*, 89, 95, 96, 96*f*, 96*t*, 97*f*, 98, 99*f*, 104*t*, 105, 105*f*, 108*f*, 109–110, 109*f*, 111*t*, 112, 113, 113*f*, 114, 116–124, 117*f*–125*f*, 126, 127, 128*f*, 128*t*, 129, 130*f*, 131, 132*f*, 133–134, 133*f*, 135*f*,

- 137, 137*f*, 138–140, 140*t*, 156, 156*f*, 158, 221*f*, 483, 600*t*, 606
Isoniazid, 46, 742, 811*t*, 813*t*
Isopropenyl vinyl ether, 96*f*
Isoproterenol, 451*t*, 452*f*, 453, 453*f*, 456–457, 474, 481, 482
Isosorbide, 540
Isosorbide dinitrate, 512
Isradipine, 487*t*
Ivabradine, 520

K

- Kainate, 57
Kcentra, 656
Ketamine, 39*f*, 44, 45, 57, 70, 74, 123, 151*t*, 176–183, 177*f*, 178*f*, 180*f*, 181*t*, 183*f*, 184*f*, 185, 249–250, 249*f*, 267, 280, 600*t*, 601, 602–603, 876–877, 899*t*, 914
Ketoconazole, 725*t*
Ketoprofen, 259*f*, 260*t*, 261*t*
Ketorolac, 251–252, 259*f*, 260*t*

L

- Labetalol, 483, 486–487, 486*f*, 500, 501*t*, 502, 504, 895*t*
Lacosamide, 339*t*, 340*t*, 342*t*, 345
Lamotrigine, 339*t*, 340*t*, 342*t*, 343, 345, 876
Lansoprazole, 727*t*
Lenalidomide, 836*t*, 849
Lepirudin, 661*f*, 663, 664
Letrozole, 829*t*, 835*t*
Leuprorelin, 829*t*, 835*t*, 847–848
Levalbuterol, 596, 596*t*
Levetiracetam, 339*t*, 340*t*, 345
Levobupivacaine, 45, 273, 274*t*, 285, 288*t*, 291–293, 292*f*, 294*f*, 295–296, 608
Levodopa, 349–352, 742
Levofloxacin, 803*t*
Levomedetomidine, 185*f*
Levomilnacipran, 856*t*, 859
Levosimendan, 466–467, 467*f*
Levothyroxine, 779
Lidocaine, 39*f*, 46, 115, 158, 174*f*, 266–267, 273*f*, 274*t*, 277, 279, 281, 281*f*, 283, 283*t*, 285–287, 288*t*, 289–292, 292*f*, 294*f*, 295–297, 464, 480, 517*t*, 518, 519*t*, 520*t*, 524–525, 604, 608, 725*t*, 901*t*, 940–941
Linagliptin, 773*t*, 777
Linezolid, 811*t*, 812*t*, 820
Liothyronine, 779
Liraglutide, 776
Lisdexamfetamine, 868
Lisinopril, 505, 506
Lispro, 771, 771*t*
Lodine. *See* Etodolac
Lomitapide, 550
Lomustine, 830*t*, 838, 839

Loratadine, 719*t*, 720*f*
Lorazepam, 162, 163, 165*t*, 170–171, 342*t*, 349, 726, 878
Lorcaserin, 706
Losartan, 506
Lovastatin, 547
Low-molecular-weight heparins (LMWHs), 660, 662, 663, 665*t*
Loxapine, 870, 870*t*
Lugol's solution, 781
Lunesta. *See* Eszopiclone
Lurasidone, 870*t*, 875
Lypressin, 794

M

Macrolides, 731, 731*f*, 811*t*, 818–819
Madopar, 352
Magnesium, 603–604
Magnesium hydroxide, 718, 726
Magnesium sulfate, 252, 602
Mannitol, 538, 540–541
Maprotiline, 867
Mechlorethamine, 830*t*, 837
Meclizine, 709*t*
Meclofenamate, 259*f*
Medroxyprogesterone acetate, 797*f*
Megestrol acetate, 829*t*, 836*t*
Meglitinides, 777
Meloxicam (Mobic), 259*f*, 260*t*
Melphalan, 830*t*, 838
Memantine, 877
Menadione, 748, 748*f*
Meperidine, 39*f*, 207*f*, 207*t*, 214*t*, 215*t*, 218–219, 725*t*, 897*t*
Mepivacaine, 44, 273, 273*f*, 274*t*, 277, 279, 281, 283, 286, 288*t*, 291, 901*t*
Meptazinol, 207*t*
Mercaptopurine, 829*t*, 832*t*, 841–842
Meropenem, 902*t*
Metaproterenol, 460*f*, 460*t*, 461, 596, 596*t*
Metformin, 772–774, 773*f*, 773*t*
Methadone, 39*f*, 45, 207*t*, 214*t*, 229, 897*t*
Methicillin, 814
Methimazole, 780–781, 781*f*
Methionine synthetase, 138, 139
Methohexital, 159, 161, 174
Methotrexate, 829*t*, 831*t*, 840, 844
Methoxamine, 80*t*
Methoxyflurane, 95, 96*f*, 104*t*, 105, 105*f*, 134
Methyldopa, 895*t*
 α -Methyldopa, 80*t*, 513
Methyl ethyl ether, 95
Methyl isopropyl ether, 95
Methylnaltrexone, 232–233, 233*f*

Methylphenidate, 355, 868
Methylprednisolone, 265*t*, 784*t*, 785, 785*f*
Methylxanthines, 355–356, 599–600
Metoclopramide, 709*t*, 712–713, 729–731, 730*t*
Metoprolol, 80*t*, 475*f*, 476*t*, 477*t*, 479, 485, 486, 501*t*, 502, 527, 895*t*
Metronidazole, 803*t*–806*t*, 808*t*, 810, 811*t*–813*t*, 820, 903*t*
Metyrapone, 791
Mexiletine, 266, 517*t*, 518, 519*t*, 520*t*, 525
Mezlocillin, 815
Midazolam, 13*f*, 14–15, 18, 35*t*, 39*f*, 40*f*, 152, 154, 154*f*, 162, 164–168, 164*f*–167*f*, 165*t*, 171, 183, 285, 600*t*, 601, 709*t*, 714, 899*t*
Mifepristone (RU 486), 796, 797*f*
Miglitol, 777
Milnacipran, 856*t*, 859
Milrinone, 465–466, 507, 606
Minocycline, 811*t*
Mipomersen, 550
Mirtazapine, 856*t*, 860–861
Mitomycin, 839
Mitomycin-C, 831*t*
Mitotane, 791
Mitoxantrone, 832*t*
Mivacurium, 46, 315*t*, 316, 316*t*, 319
Mobic. *See* Meloxicam
Moclobemide, 861
Modafinil, 356, 869
Mometasone, 598*t*
Monoamine oxidase inhibitors, 80*t*
Monoclonal antibodies, 829*t*, 834*t*, 848
Montelukast, 598*t*
Moricizine, 517*t*, 518, 520*t*
Morphine, 17, 18, 39*f*, 40, 45, 66, 70, 72, 129, 207*f*, 207*t*, 214*t*, 215–218, 215*t*, 216*f*–218*f*, 235*t*, 237*f*, 248*f*, 267, 603, 711, 898*t*, 913
Morphine-3-glucuronide, 18
Morphine-6-glucuronide, 17, 18, 45, 207*t*
Mosapride, 731
Motrin. *See* Ibuprofen
Moxifloxacin, 803*t*, 821, 903*t*

N

N₂O. *See* Nitrous oxide
Nabilone, 709*t*, 714
Nabumetone (Relafen), 260*t*
N-acetylcysteine, 877
Nadolol, 475*f*, 476*t*, 478, 483
Naftillin, 814
Nalbuphine, 207*t*, 230*f*, 231
Nalfon. *See* Fenoprofen
Nalidixic acid, 813*t*
Nalmefene, 207*t*, 231*f*

- Nalorphine, 207*t*, 230*f*
Naloxegol, 233, 233*f*
Naloxone, 39*f*, 207*t*, 231*f*, 232
Naltrexone, 207*t*, 231*f*, 232
Naprelan. *See* Naproxen
Naprosyn. *See* Naproxen
Naproxen (Naprosyn, Naprelan), 259*f*, 261*t*
Nebivolol, 476*t*, 480
Nedocromil, 598*t*, 599
Nefazodone, 856*t*, 860
Neomycin, 804*t*, 818
Neomycin–polymyxin B–gramicidin, 807*t*
Neostigmine, 80*t*, 248–249, 248*f*, 316, 322, 622
Neprilysin, 506
Nesiritide, 542
Neutral protamine Hagedorn (NPH), 771, 771*t*
Niacin (nicotinic acid), 546*f*, 547*t*, 549
Nicardipine, 487*t*, 488*f*, 488*t*, 489*t*, 492, 501*t*, 506, 507, 508
Nifedipine, 487*t*–489*t*, 488*f*, 491–492, 491*f*, 506, 725*t*, 895*t*
Niflumic acid, 259*f*
Nilutamide, 829*t*, 834*t*, 847
Nimesulide, 259*f*
Nimodipine, 487*t*, 488*f*, 489*t*, 493
Nitrates, 511–512
Nitric oxide (NO), 360–361, 507–508, 508*f*, 604–605
Nitrofurantoin, 811*t*, 813*t*
Nitrogen mustards, 830*t*, 837–838
Nitroglycerin, 25, 137, 289, 297, 501*t*, 511–512
Nitroprusside, 501*t*
Nitrosoureas, 830*t*, 838–839
Nitrous oxide (N_2O), 75, 75*f*, 95–97, 96*f*, 96*t*, 97*f*, 100*f*, 102–107, 102*f*, 104*t*, 106*f*, 108*f*, 110, 111*t*, 116–118, 120–122, 120*f*, 125–127, 128*f*, 128*t*, 129–131, 136, 138–140, 138*f*, 139*f*, 140*t*, 155, 170*t*, 600, 743
Nivolumab, 849, 850*t*
Nizatidine, 722, 722*f*, 723, 723*t*
NO. *See* Nitric oxide
Norepinephrine, 451*t*, 452–454, 452*f*, 455, 604, 609, 911
Norethindrone, 797*f*
Nortriptyline, 856*t*, 864
Noscapine, 207*f*
NPH. *See* Neutral protamine Hagedorn

O

- Obinutuzumab, 835*t*, 848
Octaplex, 656
Octreotide, 251, 792
Ocufen. *See* Flurbiprofen
Olanzapine, 870*t*, 874
Olmesartan, 506
Omeprazole, 727*t*, 728, 728*f*

Ondansetron, 709–710, 709*t*, 712
Orlistat, 706
Ouabain, 461, 462*f*
Oxacillin, 814
Oxaliplatin, 831*t*
Oxaprozin (Daypro), 261*t*
Oxazepam, 163, 168, 726
Oxcarbazepine, 339*t*, 340*t*, 342*t*, 345, 876
Oxycel, 656
Oxycodone, 39*f*, 207*t*, 229, 898*t*
Oxymorphone, 207*t*, 229
Oxytocin, 795

P

Paclitaxel, 829*t*, 833*t*, 846
Paliperidone, 874
Palonosetron, 709*t*
Pamidronate, 791
Pancuronium, 315*t*, 319, 321, 603, 622, 900*t*
Pantoprazole, 727*t*, 728
Papaverine, 207*f*
Paracetamol. *See* Acetaminophen
Paroxetine, 856*t*, 859
PCCs. *See* Prothrombin complex concentrates
Pembrolizumab, 849, 850*t*
Pemetrexed, 829*t*, 841
Penicillins, 811*t*, 813*t*, 814–815
Pentazocine, 207*t*, 230, 230*f*
Pentostatin, 832*t*, 842
Perampanel, 339*t*, 340*t*, 342*t*, 345
Perphenazine, 870, 870*t*
Pertuzumab, 834*t*, 848
Pethidine. *See* Meperidine
Phenelzine, 856*t*, 861
Phenobarbital, 17, 176, 339*t*, 341*t*, 342*t*, 345–346
Phenoxybenzamine, 471–472, 472*f*
Phentermine, 706
Phentolamine, 80*t*, 459, 471, 472*f*
Phenylephrine, 80*t*, 451*t*, 458–460, 459*f*, 474, 486, 604, 911
Phenytoin, 339*t*, 341*t*, 342*t*, 346–347, 464, 518, 526, 725*t*
Physostigmine, 711
Phytonadione, 748
Pimozide, 870, 870*t*
Pindolol, 475*f*, 476*t*, 478, 502
Pioglitazone, 773*t*, 776
Piperacillin, 815, 903*t*
Piperacillin-tazobactam, 803*t*, 808*t*
Pirbuterol, 596, 596*t*
Pirenzepine, 80*t*
Piroxicam (Feldene), 259*f*, 260*t*

Pitavastatin, 547
Plavix. *See* Clopidogrel
Polatuzumab vedotin, 835*t*, 848
Polymyxins, 811*t*
Pomalidomide, 836*t*
Pradaxa. *See* Dabigatran etexilate
Pramipexole, 352, 869
Pramlintide, 777
Pranlukast, 598*t*
Prasugrel (Effient), 668, 669, 669*t*
Pravastatin, 547
Prazosin, 80*t*, 473, 502–503
Prednisolone, 265*t*, 784*t*, 785, 785*f*
Prednisone, 265*t*, 784*t*, 785, 785*f*, 837
Pregabalin, 876
Prilocaine, 44, 273*f*, 274*t*, 277, 279, 281*f*, 283, 286, 288*t*, 289–291, 292*f*, 901*t*
Primaquine, 811*t*
Primidone, 339*t*, 341*t*, 342*t*, 347
Procainamide, 517*t*, 518, 519*t*, 520*t*, 523–524, 523*f*, 725*t*
Procaine, 272, 273*f*, 274*t*, 280, 286, 288*t*, 289, 295
Procarbazine, 837
Prochlorperazine, 709*t*
Profilnine SD, 656
Progesterone, 25, 796, 797*f*
Progesterins, 796, 797*f*, 829*t*, 847
Promethazine, 709*t*, 712, 720*f*
Propafenone, 517*t*, 519, 519*t*, 520*t*, 527
Propofol, 18, 35*t*, 37*f*–40*f*, 42, 56*f*, 57, 61, 69, 89, 123, 137, 140, 150–158, 151*f*, 151*t*, 153*f*–156*f*, 160, 161, 174, 226*f*, 285, 600*t*, 601, 603, 899*t*, 914
Propoxyphene, 207*t*
Propranolol, 17, 46, 80*t*, 131, 284, 453*f*, 464, 474–478, 475*f*, 476*t*, 477*f*, 478*f*, 482–485, 483*f*, 517*t*, 519*t*, 520*t*, 527, 528, 725*t*, 726, 726*f*
Propyl methyl ether, 96*f*
Propylthiouracil, 780–781, 781*f*
Prostacyclin, 360–361, 605, 606, 606*f*
Prostanoids, 605, 606*f*
Protamine, 477*f*, 652–653, 653*f*, 661, 662
Prothrombin complex concentrates (PCCs), 656
Pyridostigmine, 80*t*, 322, 711
Pyrilamine, 720*f*

Q

Quaternary ammonium compounds, 822–823
Quetiapine, 870*t*, 875
Quinidine, 45, 517*t*, 518, 519*t*, 520*t*, 522–523, 522*f*, 725*t*
Quinupristin-dalfopristin, 811*t*, 812*t*

R

Rabeprazole, 727*t*

Radioactive iodine, 781
Raloxifene, 796, 829*t*, 834*t*, 847
Ramipril, 506
Ramosetron, 709*t*
Ranitidine, 496, 722, 722*f*, 723, 723*t*, 725, 726
Ranolazine, 532
Rasagiline, 353
Recombinant activated factor VIIa (rFVIIa), 654–655, 655*t*
RECOTHROM, 656
Regular insulin, 771, 771*t*
Relafen. *See* Nabumetone
Remifentanil, 18, 35*t*, 39*f*, 45, 152, 207*f*, 207*t*, 215*t*, 221*f*, 225–228, 226*f*, 228*f*, 603, 898*t*
Remimazolam, 171
rFVIIa. *See* Recombinant activated factor VIIa
Rifampin, 811*t*, 812*t*, 813*t*
Riluzole, 877
Risperidone, 870*t*, 874
Rituximab, 829*t*, 834*t*, 848
Rivaroxaban (Xarelto), 661*f*, 665*t*, 666–667, 668, 896*t*
Rivastigmine, 877
RO 19-4063, 13*f*, 14–15
Rocuronium, 39*f*, 315*t*, 319, 323–324, 323*f*, 324*f*, 603, 622, 900*t*
Ropinirole, 352
Ropivacaine, 45, 249*f*, 273, 273*f*, 274*t*, 279, 283–285, 288*t*, 291–293, 291*t*, 292*f*, 296, 608, 901*t*
Rosiglitazone, 773*t*, 776
Rosuvastatin, 547
Rotigotine, 352
RU 486. *See* Mifepristone
Rufinamide, 339*t*, 341*t*, 342*t*, 347

S

Safinamide, 353
Salbutamol. *See* Albuterol
Salmeterol, 596*t*
Saxagliptin, 773*t*, 777
Scopolamine, 25, 178, 596*t*, 709*t*, 711
Selective serotonin reuptake inhibitors (SSRIs), 856*t*, 858–859
Selegiline, 353, 856*t*, 861
Semaglutide, 776
Semustine, 830*t*, 838, 839
Sertraline, 856*t*, 859
Sevoflurane, 95, 96, 96*f*, 96*t*, 97*f*, 99, 99*f*, 100*f*, 104, 104*t*, 108*f*, 109–110, 109*f*, 111*t*, 116–123, 118*f*–123*f*, 125*f*, 127–130, 128*t*, 129*f*–131*f*, 134–138, 134*f*, 135*f*, 136*f*, 140, 140*t*, 155, 158, 483, 600*t*, 606, 910
Signal transduction modulators, 829*t*, 834*t*–835*t*, 847–848
Sildenafil, 507, 606
Sildosin, 473
Silver nitrate, 823–824
Simvastatin, 547
Sinemet, 352

Sipuleucel-T, 835*t*, 849
Sitagliptin, 773*t*, 777
SNP. *See* Sodium nitroprusside
Sodium bicarbonate, 281, 718
Sodium nitroprusside (SNP), 508–511
Sodium salicylate, 259*f*
Sodium thiopental, 129*f*, 130*f*
Sonata. *See* Zaleplon
Sorafenib, 835*t*, 848
Sotalol, 517*t*, 519–520, 519*t*, 520*t*, 530–531, 895*t*
Spironolactone, 541–542
SSRIs. *See* Selective serotonin reuptake inhibitors
Statins, 546–548, 546*f*, 547*t*
Stiripentol, 339*t*, 341*t*, 342*t*, 347
Streptokinase, 671
Streptomycin, 818
Streptozocin, 838, 839
Streptozotocin, 830*t*
Succinylcholine, 18, 46, 137, 314–318, 316*t*, 900*t*, 913
Sufentanil, 35*t*, 37*f*, 39*f*, 40*f*, 45, 207*f*, 207*t*, 215*t*, 221*f*, 223–224, 223*f*, 293, 603
Sugammadex, 323–326, 323*f*, 324*f*
Sulbactam, 815
Sulfonamides, 535–536, 811*t*, 812*t*, 813*t*, 903*t*
Sulfonylureas, 774–776, 774*f*, 775*t*
Sulindac (Clinoril), 259*f*, 260*t*
Sunitinib, 835*t*, 848
Suprofen, 259*f*
Surgicel, 656

T

Tadalafil, 507, 606
Tamoxifen, 796, 796*f*, 829*t*, 834*t*, 847
Tamsulosin, 473
Taxanes, 829*t*, 833*t*, 846
Tazobactam, 815, 903*t*
Tegaserod, 731
Temazepam, 163, 171
Temozolomide, 831*t*
Teniposide, 833*t*
Terazosin, 473, 502
Terbutaline, 80*t*, 460*f*, 460*t*, 461, 596*t*, 597
Terlipressin, 794
Testosterone, 797–798, 797*f*
Tetracaine, 272, 273*f*, 274*t*, 280, 286, 288*t*, 289, 291, 293
Tetracyclines, 811*t*, 812*t*, 813*t*, 903*t*
Thalidomide, 836*t*, 849
Thebaine, 207*f*
Theobromine, 355
Theophylline, 46, 355–356, 598*t*, 599–600, 725*t*
Thioguanine, 832*t*, 842

Thiopental, 18, 27*f*, 35*t*, 40*f*, 46, 57, 129*f*, 130*f*, 152–154, 153*f*, 159, 161, 161*f*, 165, 167, 167*f*, 172–177, 173*f*, 174*f*, 175*f*, 608, 899*t*

Thioridazine, 870, 870*t*

Thiotepa, 830*t*

Thrombin JMI, 656

Tiagabine, 339*t*, 341*t*, 342*t*, 347

Ticagrelor, 668, 669, 669*t*

Timolol, 475*f*, 476*t*, 478–479, 485

Tiotropium, 596*t*, 597

Tirofiban, 670

Tisseel, 656

Tissue plasminogen activator (tPA), 671

Tizanidine, 357

Tocainide, 266, 517*t*, 518, 519*t*, 520*t*, 525

Tolazamide, 773*t*

Tolazoline, 473

Tolbutamide, 773*t*, 774*f*

Tolcapone, 352

Tolectin. *See* Tolmetin

Tolmetin (Tolectin), 259*f*, 260*t*

Tolvaptan, 543

Tomoxiprol, 259*f*

Topiramate, 339*t*, 341*t*, 342*t*, 347, 706, 877

Topoisomerase inhibitors, 829*t*, 832*t*–833*t*, 842–845, 843*f*, 844*f*, 845*t*

Topotecan, 829*t*, 833*t*

Toremifene, 829*t*, 834*t*, 847

Torsemide, 538

tPA. *See* Tissue plasminogen activator

Tramadol, 207*t*, 229–230, 250

Tranexamic acid (TXA), 651–652, 941, 941*f*

Tranylcypromine, 856*t*, 861

Trastuzumab, 829*t*, 834*t*, 848

Trazodone, 856*t*, 860

Treprostинil, 605

Triamcinolone, 265*t*, 598*t*, 784*t*, 785*f*, 786

Triamterene, 541

Triazenes, 831*t*

Triazolam, 163, 725*t*

Trichloroethylene, 96*f*

Tricyclic antidepressants, 46, 80*t*, 82, 864

Trihexyphenidyl, 353

Trilisate. *See* Trisalicylate

Trimethaphan, 513

Trimethoprim, 811*t*, 812*t*, 813*t*

Trimethoprim-sulfamethoxazole, 808*t*, 811*t*, 812*t*

Trisalicylate (Trilisate), 261*t*

Tropisetron, 709*t*, 710

Tubocurarine, 45, 80*t*, 315*t*, 321

Tubulin-binding drugs, 829*t*, 833*t*, 845–846

TXA. *See* Tranexamic acid

Tylenol. *See* Acetaminophen

U

- Unfractionated heparin, 660, 661, 665*t*
- Urea, 540
- Urokinase, 671

V

- Valproic acid, 339*t*, 341*t*, 342*t*, 347–348, 876
- Valsartan, 506
- Vancomycin, 803*t*, 804, 805*t*–809*t*, 810, 810*f*, 811*t*, 819–820, 903*t*
- Vardenafil, 507
- Varenicline, 878
- Vasopressin, 285, 604, 793–794, 940
- Vecuronium, 315*t*, 319, 323–324, 603, 900*t*
- Venetoclax, 835*t*, 848
- Venlafaxine, 856*t*, 859
- Verapamil, 183, 487*t*–489*t*, 488*f*, 489–491, 491*f*, 493, 494, 495*f*, 506, 517*t*, 519*t*, 520, 520*t*, 531–532
- Vigabatrin, 339*t*, 341*t*, 348
- Vilazodone, 856*t*, 860
- Vildagliptin, 773*t*, 777
- Vinblastine, 833*t*, 845–846
- Vinca alkaloids, 829*t*, 833*t*, 845–846
- Vincristine, 829*t*, 833*t*, 837, 845–846
- Vindesine, 845
- Vinorelbine, 829*t*, 833*t*, 845–846
- Vitamin K antagonists, 664–666, 665*t*
- Voltaren. *See* Diclofenac
- Vortioxetine, 856*t*, 860

W

- Warfarin, 664–666, 665*t*, 668, 725*t*, 896*t*, 905

X

- Xarelto. *See* Rivaroxaban
- Xenon, 99–100, 100*f*, 104*t*, 111*t*, 137
- Ximelagatran, 667

Y

- Yohimbine, 80*t*, 472

Z

- Zafirlukast, 598*t*
- Zaleplon (Sonata), 172, 878
- Ziconotide, 250
- Zileuton, 598*t*, 599
- Ziprasidone, 870*t*, 875
- Zoledronate, 791
- Zolpidem (Ambien), 172, 878

Zomepirac, 259*f*
Zonisamide, 339*t*, 341*t*, 342*t*, 348
Zopiclone, 878

Note: Page numbers followed by *f* indicate figures; page numbers followed by *t* indicate tables.

A

- A-aD_{O₂}. *See* Alveolar-arterial oxygen difference
- Abnormal breathing patterns, 584
- Abnormal involuntary movements, levodopa and, 351
- ABO compatibility, 640
- Absolute refractory period, 52
- Absorption, 22
 - of local anesthetics, 277, 277*f*
 - route of administration and, 24–25
- Absorption pharmacokinetics, 30
- Abuse potential
 - of GABA agonists, 157
 - of opioids, 233, 238
- Acceleromyography, 329, 329*f*
- Accessory pathway conduction, with inhaled anesthetics, 123
- ACE, in lungs. *See* Angiotensin-converting enzyme, in lungs
- ACE inhibitors. *See* Angiotensin-converting enzyme inhibitors
- Acetylcholine
 - in epinephrine release, 86
 - in excitatory ligand-gated ion channels, 56–57
 - metabolism of, 83–84
 - as neurotransmitter, 53, 53*t*, 82–84
 - receptors for, 83
 - storage and release of, 83
 - synthesis of, 82–83
- Acetylcholine receptor agonists, 877–878
- Acetylcholinesterase, 308, 314
 - neuromuscular-blockade reversal, 322–323
 - structure of, 308*f*
- Acetylcholinesterase inhibitors, 877
 - for dementia, 877–878
 - limitations of, 322–323
 - mechanism of action of, 322
 - neuromuscular function monitoring with, 326
 - pharmacokinetics of, 322
 - side effects of, 322
- Achalasia, 690
- Acid-base balance, 422
- Acid-base disturbances
 - anion gap and, 624, 624*t*
 - classification of, 621, 621*t*
 - compensation for, 624–625
 - metabolic acidosis, 621*t*, 622–624, 624*t*, 625
 - with GABA agonists, 156–157
 - with TPN, 738
 - metabolic alkalosis, 621*t*, 624, 625

respiratory acidosis, 621–622, 621*t*, 624–625
respiratory alkalosis, 621*t*, 622, 625
temperature and, 625–626, 625*t*
Acid-base effect, carbon dioxide and, 384
Acidosis
dilutional, 623, 623*t*
lactic, 622–623, 773–774
with GABA agonists, 156–157
massive transfusion coagulopathy and, 677
metabolic, 621*t*, 622–624, 624*t*, 625
with GABA agonists, 156–157
with TPN, 738
respiratory, 621–622, 624–625
Acid rebound, 718
Acinar airways, 557
ACTH. *See* Adrenocorticotrophic hormone
Action potential, 49, 51–52
abnormal, 52
cardiac, 395–396
elements of, 51*f*
ion channel evaluation, 52
propagation of, 52, 59*f*
Activated clotting time (ACT), 661
Activated partial thromboplastin time (aPTT), 633, 660–661
Acute adrenal insufficiency, corticosteroids for, 786
Acute coronary syndrome, β -adrenergic receptor antagonists for, 484
Acute hemorrhage, 89
Acute kidney injury (AKI), 423–426
classification of, 423–424, 424*f*
diagnosis of, 424–426, 425*f*
intrinsic causes of, 423–424, 424*f*
Acute lung injury, transfusion-related, 646–648, 646*f*, 647*t*
S-Adenosylmethionine, 750*t*
Adenyl cyclase, 54, 54*f*
Adhesives, fibrin tissue, 656
Adjunctive agents, airway and, 602
Adoptive cellular therapy, 849–851
Adrenal cortex, 759–762, 760*t*
Adrenal medulla, 86
Adrenergic fibers, 81, 82
 α_2 -Adrenergic receptor agonists, 246–248, 472, 473–474, 503–505, 503*f*
 β_2 -Adrenergic receptor agonists. *See also* Selective β_2 -adrenergic receptor agonists
for airway
inhaled, 595–596, 596*t*
systemic, 596–597
 α -Adrenergic receptor antagonists, 471–473, 472*f*, 501–502
 β -combined with, 486–487, 486*f*
 α_1 -Adrenergic receptor antagonists, 501*t*, 502–503
 β -Adrenergic receptor antagonists, 474–486, 501–502, 501*t*, 519, 521, 527–528
classification of, 474, 476*t*, 477*t*
clinical uses of, 483–486, 484*t*, 485*t*

α -combined with, 486–487, 486*f*
hyperkalemia with, 445
lithium and, 880*t*
mechanism of action of, 474, 501–502
pharmacokinetics of, 474–475, 477–478, 479, 480–481
side effects of, 477, 481–483, 483*f*
structure-activity relationships of, 474, 475*f*
 α_2 -Adrenergic receptors, 246
 β_2 -Adrenergic receptors, 54*f*
Adrenocortical suppression, with GABA agonists, 161, 161*f*
Adrenocorticotropic hormone (ACTH), 754*t*, 756–757, 756*t*, 761–762, 792
Adults
blood:gas partition coefficients in, 105, 105*f*
gas exchange in, 588
inhaled anesthetics in, 102, 102*f*
Afferent nerve fibers, classification of, 49–50, 50*t*
Afterload, 398–399, 399*f*
Aging. *See also* Elderly patients
benzodiazepines and, 163–164
blood:gas partition coefficients and, 105, 105*f*
gas exchange and, 588
MAC of inhaled anesthetics and, 112
neurophysiology of, 930–931
pain and, 931
Agonists, 12, 13*f*, 14, 14*f*
Agranulocytosis, with antimicrobials, 811*t*
Air-blood barrier, 561*f*
Airway
adjunctive agents and, 602
 β -adrenergic agonists for
inhaled, 595–596, 596*t*
systemic, 596–597
anesthetics and, 600–602, 600*t*
anticholinergics for
inhaled, 596*t*, 597
systemic, 596*t*, 597
autonomic nervous system influence on, 595–597, 596*t*
inflammation and, 597–600, 598*t*
inhaled corticosteroids, 598–599, 598*t*
leukotriene modifiers for, 598*t*, 599
mast cell stabilizers, 598*t*, 599
methylxanthines, 598*t*, 599–600
systemic corticosteroids, 599
maternal, 906–907, 907*t*
pharmacology of, 595–602
Airway compliance, 568–570, 570*f*, 571*f*
Airway irritability
with GABA agonists, 158
inhaled anesthetics and, 129–130, 129*f*–131*f*
Airway resistance, 570–573, 571*f*
 β -adrenergic receptor antagonists and, 478, 479, 482

inhaled anesthetics and, 129–130, 129*f*–131*f*
AKI. *See* Acute kidney injury
Albumin, 687, 704
Albumin solution, 434, 435*t*
Alcohols, 821–822
Aldosterone, 759–760, 760*t*, 783, 784*f*, 784*t*
Aldosterone receptor antagonists, 537*t*, 541–542
Alkalosis
metabolic, 621*t*, 624, 625
respiratory, 621*t*, 622, 625
Alkylating agents, 829*t*, 830*t*–831*t*, 836–839
Alkyl sulfonates, 830*t*, 838
Allergic reactions
to antimicrobials, 811*t*, 813*t*
to barbiturates, 176
to GABA agonists, 156, 161
to heparin, 662
to insulin replacement, 772
to local anesthetics, 282
to neuromuscular-blocking drugs, 321
to non- γ -aminobutyric acid sedative-hypnotics, 182
to opioids, 233
to penicillins, 816
Allergic therapy, 786
Allodynia, 196
Alloimmunization, 641, 642
Alveolar-arterial oxygen difference (A-aD_{O₂}), 579, 926–927, 926*f*
Alveolar macrophages, 559, 562, 562*f*
Alveolar partial pressure, of inhaled anesthetics, 101–103, 101*t*
alveolar ventilation, 102–103, 102*f*, 103*f*
anesthetic breathing system, 103
inhaled partial pressure, 101–102, 101*f*, 102*f*
Alveolar-to-venous partial pressure differences, inhaled anesthetics and, 107–108, 107*t*
Alveolar ventilation, inhaled anesthetics and, 102–103, 102*f*, 103*f*
Alveoli, 557–562, 562*f*
Ames test, 138
Amino acids, 687, 702–704, 703*f*, 703*t*
 γ -Aminobutyric acid (GABA), 49, 53, 53*t*
in inhibitory ligand-gated ion channels, 57
 γ -Aminobutyric acid (GABA) agonists, 150–161, 151*f*, 151*t*, 153*f*–156*f*, 160*f*, 161*f*, 878
 γ -Aminobutyric acid (GABA) receptor, 14–15, 57, 69, 162, 162*f*, 251
Anaerobic glycolysis, 700
Analeptics, 354–356
Analgesia
corticosteroids for, 787
GABA agonists, 154
magnesium and, 441
neuraxial, 179
non- γ -aminobutyric acid sedative-hypnotics, 178–179
patient-controlled
nausea and vomiting with, 250

opioids for, 234, 235*f*, 235*t*
regional, pulmonary circulation and, 604
thoracic epidural, 604
Analgesics, 257
centrally acting nonopiod, 246–252
 α_2 -adrenergic receptor agonists, 246–248
conopeptides, 250–251
cyclooxygenase inhibitors, 251–252
peripherally acting, 257
capsaicin, 267
opioids, 268
systemic local anesthetics, 264–267
Anatomic dead space, 576
Androgens, 762–763, 797–798, 797*f*, 798*f*, 847
Anemia
in massive transfusion coagulopathy, 676
megaloblastic, 743
Anesthesia. *See also* Inhaled anesthetics; Local anesthetics
awareness and recall during, 62
barbiturates in, 172–173
and cortisol and ACTH secretion, 761–762
dissociative, 156
in elderly patients, 924
epidural, with local anesthetics, 292–293, 292*f*
gas exchange under, 584–585
general, 150
opioid antagonist and, 232
hypotension during, 794
induction of, 155, 156, 156*f*, 158, 159
barbiturates for, 174, 174*f*
benzodiazepines for, 167, 167*f*
GABA agonists for, 152
non- γ -aminobutyric acid sedative-hypnotics for, 179–180
kidneys and, 426–429
lithium and, 880
maintenance of
benzodiazepines for, 167
GABA agonists for, 153
MAO inhibitors and, 863–864
perioperative temperature changes during, 89–90, 90*f*
regional, with local anesthetics, 287–297, 288*t*–289*t*
renal blood flow and, 427–429, 427*f*, 428*t*
spinal, with local anesthetics, 293, 294*f*
SSRIs and, 859
topical, with local anesthetics, 288*t*–289*t*, 289
Anesthetic breathing system, 103
Anesthetic preconditioning, with inhaled anesthetics, 126–127, 126*f*
Anesthetics
 β -adrenergic receptor antagonists and, 483
airway and, 600–602, 600*t*
calcium channel blockers and, 494, 495*t*

in fetus, 914–915
inhaled. *See* Inhaled anesthetics
local. *See* Local anesthetics
maternal use of, 901*t*
pulmonary circulation and, 602–603
total, 115
opioids for, 234
volatile
airway and, 600–601, 600*t*
pulmonary circulation and, 603
Angina pectoris, β -adrenergic receptor antagonists for, 484
Angiotensin-converting enzyme (ACE), in lungs, 608–609, 609*f*
Angiotensin-converting enzyme (ACE) inhibitors, 505–506, 794
lithium and, 880*t*
NSAIDs and, 262
Angiotensin II receptor inhibitors, 505–506, 794
Anion gap, 624, 624*t*
ANP. *See* Atrial natriuretic peptide
ANS. *See* Autonomic nervous system
Antacids, 717–719
Antagonists, 12, 13*f*, 14, 14*f*
Anterior commissure, 61
Anterior pituitary gland
drugs for, 792
hormones of, 754*t*, 755–757, 755*f*, 755*t*, 756*t*
Anterior spinal artery syndrome, with local anesthetics, 287
Anthracenediones, 832*t*
Anthracyclines, 829*t*, 832*t*
Antiandrogens, 829*t*, 834*t*, 847
Antiarrhythmic drugs, 516
classification of, 516–520, 517*t*–520*t*
effects of, 518, 518*t*
efficacy of, 521
mechanism of action, 516–517, 517*f*
pharmacology of, 522–532
proarrhythmic effects of, 521
prophylactic, 521–522
Antibiotics
antitumor, 829*t*, 833*t*, 842–845
maternal use of, 902*t*–903*t*
nondepolarizing neuromuscular block and, 320
Anticholinergic delirium, 865
Anticholinergic effects, of tricyclic antidepressants, 864–865
Anticholinergics
for airway
inhaled, 596*t*, 597
systemic, 596*t*, 597
levodopa and, 352
overdose of, 711–712
for Parkinson disease, 353
for PONV, 709*t*, 711–712

tricyclic antidepressants and, 866
Anticholinergic syndrome, 858*t*
Anticoagulants, 656, 660–671
danaparoid, 663
direct thrombin inhibitors, 663–664, 664*t*
fondaparinux, 662–663
heparin, 660–662, 661*f*
LMWHs, 662
maternal use of, 896*t*
oral, 664–668
direct factor Xa inhibitors, 665*t*, 666–667
direct thrombin inhibitors, 667
perioperative management of, 667–668
vitamin K antagonists, 664–666, 665*t*
platelet inhibitors, 668–670, 669*t*, 670*f*, 671*f*
thrombolytic drugs, 671
Anticonvulsants
benzodiazepines, 170, 170*f*
for bipolar disorders, 876
GABA agonists, 153
glutamate antagonists, 876
lithium and, 880*t*
nondepolarizing neuromuscular block and, 320
Antidepressants
adverse effects of, 855–858, 856*t*
glutamate antagonists, 876–877
MAO inhibitors, 861–864
serotonin and norepinephrine multimodal drugs, 860–861
serotonin multimodal drugs, 860
serotonin reuptake inhibitors, 855–860
serotonin syndrome, 219, 857–858, 858*t*
tricyclic antidepressants, 859–860, 864–867
Antidiuretic hormone, 53*t*, 369
Antiemesis
with antipsychotic drugs, 870–871
corticosteroids for, 787
GABA agonists, 153
with gastrointestinal prokinetics, 730
Antiepileptic drugs, 337–349, 339*t*
dosing of, 338, 339*t*
major, 339*t*–342*t*, 343–349
mechanism of action of, 338–342
pharmacokinetics of, 337–338, 342*t*
accelerated metabolism and, 338
protein binding and, 337–338
plasma concentrations of, 338
side effects of, 340*t*–341*t*, 343–349
status epilepticus, 349
Antiestrogens, 796, 796*f*, 829*t*, 834*t*, 847
Antifibrinolytic agents
aprotinin, 652

lysine analogs, 651–652
for massive transfusion coagulopathy, 680
Antihistamines, 719–727
airway and, 602
 H_1 -receptor antagonists, 719–722, 719*t*, 720*f*
 H_2 -receptor antagonists, 722–727, 722*f*, 723*t*–725*t*, 726*f*, 727*f*
for PONV, 709*t*, 712
Antihypertensive drugs, 501*t*
maternal use of, 895*t*
tricyclic antidepressants and, 866
Antiinflammatory effects
of cortisol, 761
of spinal anesthesia, 295–296
Antimetabolites, 829*t*, 831*t*–832*t*, 840–842
Antimicrobials
drug toxicity with, 811*t*–812*t*
in perioperative period, 814–821
selection of, 810–812
special patient groups for, 812–814
for surgical prophylaxis, 802–803, 803*t*–809*t*, 810*f*
Antineoplastic drugs. *See* Chemotherapeutic drugs
Antioxidant properties, of GABA agonists, 157–158
Antiplatelet drugs, maternal use of, 896*t*
Antiprogestins, 796, 797*f*
Antipruritic, GABA agonists, 153
Antipsychotic drugs
dopamine antagonists as, 869–873
drug interactions with, 873
levodopa and, 351
mechanism of action of, 869
metabolism of, 870
pharmacokinetics of, 870
side effects of, 871–873
Antiseptic prophylaxis, 821–824
Antithrombin, 632
Antitumor antibiotics, 829*t*, 833*t*, 842–845
Anxiolytics, 150
Aorta, 376*t*
Aortic insufficiency, 402, 403*f*
Aortic stenosis, 401–402
Aortocaval compression, maternal, 906
Apnea, with spinal anesthesia, 295
aPTT. *See* Activated partial thromboplastin time
Aquaporins (AQP), 9, 418
modulators of, 537*t*, 543
Arachidonic acid, 700, 700*f*
metabolites in lungs, 610
Arachnoid villi, 70, 71*f*
Arginine vasopressin (AVP), 754*t*, 757–758, 757*t*, 793–795
Aromatase inhibitors, 829*t*, 835*t*, 847–848
Arrhythmia, mechanisms of, 404–405, 405*f*

Arteries, 359
anatomy of, 376*f*, 376*t*
pulse pressure in, 362–363, 362*f*
Arterioles, 359–360, 375, 376*f*, 376*t*
Arthralgias, with antimicrobials, 812*t*
Arthritis, corticosteroids for, 788
Ascites, 380, 688
Ascorbic acid (vitamin C), 740*t*, 741*f*, 744–745
Aspiration pneumonitis, 787
Asthma
combination therapy for, 600, 600*t*
corticosteroids for, 598–599, 786–787
leukotriene modifiers for, 599
magnesium and, 441
mast cell stabilizers for, 599
methylxanthines for, 599–600
Ataxia, 64
Atelectasis, 567, 569*f*
ATPase. *See* Sodium-potassium pump
Atrial fibrillation, 409–410, 410*f*, 522
Atrial flutter, 410, 410*f*
Atrial natriuretic peptide (ANP), 421, 537*t*, 542
Atrial paroxysmal tachycardia, 409, 410*f*
Atrial reflexes, 370
Atrioventricular (AV) node, 390, 391, 391*f*
Auditory cortex, 60
Auditory evoked potentials, 70
Auscultation measurement, of blood pressure, 361
Autonomic nervous system (ANS), 77–86
acetylcholine in, 82–84
adrenal medulla, 86
airways and, 595–597, 596*t*
anatomy of, 78–80, 81*f*, 82*f*, 83*f*
denervation hypersensitivity, 86
diabetic autonomic neuropathy, 85
dysfunction of, 84–85, 85*t*
mechanism of drugs on, 80*t*
neuromuscular-blocking drugs and, 321
norepinephrine in, 81–82, 84*f*
parasympathetic, 77–78
physiology of, 81–84, 84*f*
residual tone of, 84
responses to stimulation of, 78, 79*t*
sympathetic, 77–78
tissue blood flow control by, 368
Autonomic reflexes, 66
Auto-PEEP, 590
Autoregulation
of CBF, 67*f*, 67*t*, 68
of renal blood flow, 419–420, 419*f*
AVP. *See* Arginine vasopressin

Awareness
during anesthesia, 62
with inhaled anesthetics, 117
Axons. *See* Nerve fibers
Axon terminal, 53f
Azotemia, 423

B

Babinski sign, 65
Bacterial growth, with GABA agonists, 157
Barbiturates, 172–176
in anesthesia, 172–173
ionization of, 23
mechanism of action of, 173
pharmacodynamics of, 173–175, 174*f*, 175*f*
pharmacokinetics of, 173–176, 173*f*–175*f*
side effects of, 175–176, 175*f*
tolerance to, 46
Barometric pressure, gas exchange and, 587
Baroreceptor reflexes, 369, 369*f*, 370*f*
Barrier pressure, decreased, 712
Basal ganglia, 63
Base excess (BE), 623–624
Benzamides, for PONV, 712–713
Benzodiazepines, 161–172, 162*f*
for anxiety, 878
and awareness, 62
for epilepsy, 343
mechanism of action of, 162–163, 162*f*
metabolism of, 165, 165*f*, 168, 168*f*
pharmacokinetics of, 164–165, 165*t*, 168–169, 168*f*, 171
for PONV, 709*t*, 714
receptor for, 13*f*, 14, 57, 69
short-acting nonbenzodiazepine, 172
side effects of, 163–164
specific drugs, 164–172, 164*f*–170*f*, 165*t*, 170*t*
Benzothiazepines, 493–494
Benzylisoquinolinium compounds, 315*t*, 318–319, 321
Bezold–Jarisch reflex, 370
Bicarbonate buffering systems, 618–619, 618*f*, 619*f*
Bier block, 291–292, 292*f*
Biguanides, 773*t*
Bile acid resins, 546*f*, 547*t*, 548–549
Bile salts, 686
Biliary tract, opioids and, 212
Bilirubin, 686, 686*f*
antimicrobials and, 811*t*
Bioavailability, 30
Biogenic amines, in lungs, 609–610
Biologic glue, 656

Biomarkers, for acute kidney injury, 426
Bioreductive alkylating drugs, 831*t*
Biotin, 740*t*, 742
Bipolar disorders
anticonvulsants for, 876
lithium for, 878
Bisphosphonates, 442–443, 443*f*, 791
Bitemporal hemianopia, 73
Black cohosh, 749*t*
Bladder, urine transport to, 419
Bleeding risk, serotonergic drugs and, 857
Blindness, postoperative, 73
Blood-brain barrier, 72
peripheral analgesics and, 257
Blood components, 636–648, 638*t*
fresh frozen plasma, 636, 638*t*, 639–641
HAE and C1 INH, 645
platelet concentrates, 636, 638*t*, 641–644, 642*t*
purified protein concentrates, 644–645
red blood cells, 637–639, 638*t*
Blood flow
in capillaries, 377
cerebral, 67–68, 67*f*, 67*t*
with inhaled anesthetics, 117–118, 117*f*, 118*f*
nitrodilators and, 509–510
cutaneous, 89
in gastrointestinal tract, 688
hepatic, 684, 684*f*
control of, 685
with inhaled anesthetics, 131, 131*f*
in lungs, 384, 385*f*
pulmonary, 382–384, 382*f*. *See also* Cardiac output
renal, 419–420, 419*f*, 420*f*
anesthesia and, 427–429, 427*f*, 428*t*
in skeletal muscles, 310–311
tissue. *See* Tissue blood flow
uterine, 911
Blood:gas partition coefficients
of inhaled anesthetics, 104–105, 104*t*, 105*f*
of nitrous oxide, 105–106, 106*f*
Blood pressure. *See also* Systemic blood pressure
auscultation measurement of, 361
during and after cardiopulmonary bypass, 363–364, 363*f*
measurement of, 361
normal, 360, 361*t*
progressive declines in, 361–362, 361*f*
Blood viscosity, 366, 366*f*
Blood volume, 1–2, 382*f*
maternal, 904–905, 904*f*
pulmonary, 382
regulation of, 420–421

Body fluids, 1
by age and gender, 1, 2*t*
compartments of, 2*f*
constituents of, 2, 3*f*
composition of, 431, 432*f*
of neonates, 891–892
osmolarity of, 421–422, 421*f*
osmosis of, 2–3, 3*f*
regulation of, 420–423, 421*f*, 422*f*
tonicity of, 3, 4*f*
volume of, 1–2

Body temperature. *See also* Thermoregulation
increased, causes of, 88–89, 88*t*
regulation of, 87–89

Bolus dosing, 33–35, 34*f*, 35*t*

Bolus pharmacokinetics, 27–29, 28*f*

Bone composition, 442–444, 443*f*

Bone marrow function
antimicrobials and, 811*t*
inhaled anesthetics and, 138–139, 139*f*

Bowel segment pressures, with inhaled anesthetics, 100, 100*f*

Bowman capsule, 415, 416*f*

Bradycardia-related death, 155, 155*f*

Bradykinin, 609

Brain, 59, 60*f*
Brain natriuretic peptide, 537*t*, 542

Brainstem, 59, 60*f*, 62–64
basal ganglia, 63
limbic system and hypothalamus, 63
reticular activating system, 63

Brain waves
classification of, 68–69, 68*f*
monitoring of, 69

Breathing. *See also* Spontaneous breathing
abnormal patterns of, 584
anesthetic system, 103
effect of, 384
in elderly patients, 927
with inhaled anesthetics, 127
non- γ -aminobutyric acid sedative-hypnotics and, 185
sleep-disordered, 586–587, 927
work of, 573–574

Bronchial circulation, 381

Bronchoconstriction
acetylcholinesterase inhibitors, 322
GABA agonists and, 153–154, 153*f*
with inhaled anesthetics, 129, 130, 130*f*

Bronchodilation
with epinephrine, 452
with inhaled anesthetics, 129, 129*f*
with spinal anesthesia, 296

Bronchomotor tone, 182
Bronchoscopy simulator, 557, 560*f*
Bronchus
 asthmatic, 601*f*
 structure of, 556–557, 557*f*, 558*f*, 559*f*
Buccal administration, 25
Buffered diffusion, 320
Buffer systems, 617–619, 618*f*, 618*t*
bicarbonate, 618–619, 618*f*, 619*f*
 hemoglobin, 619
 phosphate, 619
 protein, 619
Bullae, 589, 589*f*
Bundle branch block, 406, 407*f*, 408*f*
Bundle branches, 390, 391*f*
Bundle of His, 390, 391*f*
Butyrophenones, for PONV, 713
Butyrylcholinesterase, 314
 activity of, 315–316
 genetic variants of, 316–317, 316*t*

C

C1 esterase inhibitor (C1 INH), 645
CABG. *See* Coronary artery bypass graft
Calciferol, 740*t*, 745*f*, 746–747
Calcitonin, 759
Calcium, 466–467
 in intravenous fluids, 441–444, 443*f*
 in ion channels, 55
 measurement of, 466
 plasma concentration of, 423
 regulation of, 791–792
 role of, 441
 sensitizers for, 466–467, 467*f*
Calcium channel blockers, 487–496, 488*f*, 501*t*, 506–507, 520, 521–522, 531–532
benzothiazepines, 493–494
 classification of, 487*t*
 clinical uses of, 491, 492, 493
 dihydropyridines, 491–493, 506–507
 drug interactions with, 494–496, 495*f*, 495*t*
 glutamatergic drugs as, 876
 mechanism of action of, 487–488, 490*f*
 pharmacokinetics of, 488*t*, 489, 489*t*, 491, 492, 493–494
 phenylalkylamines, 490–491, 491*f*
 side effects of, 490–491, 492
Callus, 442
cAMP. *See* Cyclic adenosine monophosphate
Camptothecins, 833*t*
Cannabinoids, 881
 for PONV, 709*t*, 714

Cannabis, 881
Capillaries, 360
anatomy of, 375–377, 376*f*, 376*t*, 377*t*
blood flow in, 377
endothelium of, 377–379
fluid movement between interstitium and lumen of, 377–379
glomerular, 416*f*, 419
peritubular, 417, 419
pulmonary, 562*f*
Capsaicin, 267
Carbohydrate metabolism, 686, 697–700, 699*f*
Carbon dioxide (CO_2)
and acid-base effect, 384
blood transport of, 581–583, 582*f*
and cerebral physiology, 67–68, 67*t*
ventilatory response to, with inhaled anesthetics, 127, 127*f*, 128*f*
Carbonic anhydrase inhibitors, 535–536, 536*f*, 537*t*
Carbon monoxide poisoning, intraoperative diagnosis of, 98–99
Carboxyhemoglobin (COHb), 98, 581
Carcinoid syndrome, 742
Cardiac action potential, 395–396
Cardiac arrest, 294–295
corticosteroids for, 789
resuscitation and, 935, 936–938, 939
with spinal anesthesia, 294–295
vasopressin for, 794
Cardiac arrhythmias. *See also* Antiarrhythmic drugs
treatment for, 522
Cardiac conduction system, 390–395, 391*f*–395*f*, 392*t*
Cardiac cycle
electrical and mechanical events of, 397–398, 397*f*, 398*f*
hemodynamic calculations, 399–400, 400*t*
myocardial performance, preload, and afterload, 398–399, 398*f*, 399*f*
Cardiac disease, inhaled anesthetics and, 125
Cardiac dysrhythmias, 403–411
 β -adrenergic receptor antagonists for, 485–486
etiology of, 403–404
inhaled anesthetics and, 122–123, 123*f*
levodopa and, 351
magnesium and, 440–441
mechanism of arrhythmia, 404–405, 405*f*
spinal anesthesia and, 295
types of, 405–411, 405*t*
atrial fibrillation, 409–410, 410*f*
atrial flutter, 410, 410*f*
atrial paroxysmal tachycardia, 409, 410*f*
bundle branch block, 406, 407*f*, 408*f*
heart block, 406, 406*f*, 407*f*
nodal paroxysmal tachycardia, 409
preexcitation syndrome, 407, 408*t*
premature atrial contractions, 409, 409*f*

premature ventricular contractions, 410, 411*f*
reentry, 407
sinus bradycardia, 408, 409*f*
sinus dysrhythmias, 409, 409*f*
sinus tachycardia, 408, 408*f*
ventricular fibrillation, 411, 411*f*
ventricular tachycardia, 411, 411*f*
Cardiac function, control of, 396–397
Cardiac glycosides, 461–464, 462*f*, 463*f*
Cardiac muscle, 305
Cardiac output
determinants of, 372, 398, 398*f*
hemodynamic calculations for, 399–400, 400*t*
inhaled anesthetics and, 106–107, 121, 121*f*
maternal, 905, 906*f*
measurement of, 374–375, 374*f*
pressure-volume loops, 373, 373*f*
pulmonary arterial pressure and, 382, 382*f*
regulation of, 371–375
shock syndromes, 373–374
ventricular function curves of, 372–373, 372*f*
Cardiac physiology
anatomy
of heart, 388–395, 389*f*, 392*t*
of pericardium, 388
myocardium, 395–397, 396*f*
Cardiac protection, with inhaled anesthetics, 126–127, 126*f*
Cardiomyocytes, 395, 396*f*
Cardiomyopathy
chemotherapeutic antibiotics and, 843, 843*f*
cirrhotic, 685
Cardiopulmonary bypass (CPB), 221
benzodiazepines and, 164–165
GABA agonists and, 159
inhaled anesthetics and, 106
MAC, 111
opioid agonists and, 221
systemic blood pressure during and after, 363–364, 363*f*
Cardiopulmonary resuscitation, 935, 939–941, 939*f*
Cardiovascular depression
 β -adrenergic receptor antagonists and, 482
inhaled anesthetics and, 121, 122, 125–126
Cardiovascular system
acetylcholinesterase inhibitors and, 322
 α -adrenergic receptor agonists and, 504
 α -adrenergic receptor antagonists and, 503
 β -adrenergic receptor antagonists and, 476*t*, 477, 477*t*, 481–482
antipsychotic drugs and, 872
benzodiazepines and, 166, 169, 170*t*
dopamine and, 456
of elderly patients, 921–924, 922*f*, 923*t*

ephedrine and, 458
epinephrine and, 450–452
GABA agonists and, 154–155, 154f, 155f, 159–160, 160f
levodopa and, 350–351
lithium and, 879
local anesthetics and, 283–284, 284f
maternal, 894–906, 904t
of neonates, 889–890, 890f
nitrodilators and, 509
non- γ -aminobutyric acid sedative-hypnotics and, 181–182, 181t
NSAIDs and, 259
opioid agonists and, 222, 222f
opioids and, 209–210, 210f, 211f
phenylephrine and, 459, 459f
succinylcholine and, 317
tricyclic antidepressants and, 865
Catecholamines
aging and, 924
in cardiopulmonary resuscitation, 939–940, 939f
enzymatic synthesis of, 84f
naturally occurring, 450–456
dopamine, 451t, 452f, 454–456
epinephrine, 450–453, 451t, 452f
in lungs, 609
norepinephrine, 451t, 452f, 453–454
synthetic, 451t, 456–458
Catechol-*O*-methyltransferase (COMT), 82
Catechol-*O*-methyltransferase (COMT) inhibitors
for Parkinson disease, 352
side effects of, 352
Cauda equina, 64
Cauda equina syndrome (CES), 286–287
CBF. *See* Cerebral blood flow
CC. *See* Closing capacity
Cells, 4–11
anatomy of, 5, 5f
membrane of, 5–9, 5t, 6f
molecular transfer through, 6–9, 7f, 8f
Central anticholinergic syndrome, 711
Centrally acting muscle relaxants, 356–357
Centrally acting nonopioid analgesics, 246–252
 α_2 -adrenergic agonists, 246–248
conopeptides, 250–251
cyclooxygenase inhibitors, 251–252
Central nervous system (CNS), 59–76
 β -adrenergic receptor antagonists and, 483
benzodiazepines and, 165–166, 166f
brainstem, 59, 60f, 62–64
cerebellum, 60f, 63–64
cerebral blood flow, 67–68, 67f, 67t
cerebral hemispheres, 60–62, 60f

cerebrospinal fluid, 70–72
corticosteroids and, 791
electroencephalogram of, 68–70, 68*f*
epilepsy, 69, 337, 338*t*, 343
GABA agonists and, 154, 154*f*, 159
hearing, 74–75, 74*f*
imaging of, 66–67
inhaled anesthetics and, 116–119, 117*f*, 118*f*, 130
ischemic reflex, 370
local anesthetics and, 282–283, 283*t*
maternal, 904*t*, 909–910
nausea and vomiting, 75–76, 75*f*
non- γ -aminobutyric acid sedative-hypnotics and, 180–181, 180*f*
opioids and, 211
neuraxial, 237
pain and, 196, 198*f*
ascending pathway for, 200
central sensitization, 199–200
descending pathway for, 200–201
dorsal horn, 197–199, 198*f*
gate theory for, 199, 199*f*
supraspinal modulation, 200
in respiratory control, 583–584, 583*f*
smell, 75
spinal cord, 59–60, 64–67, 64*f*, 65*f*, 66*f*
stimulants of, 354–356
systemic local anesthetics and, 266
taste, 75
tricyclic antidepressants and, 865
vision, 72–74, 72*f*, 73*f*
Central sensitization, 199–200
Central venous pressure (CVP), 364–365
Cerebellar nystagmus, 64
Cerebellum, 60*f*, 63–64, 71*f*
dysfunction of, 64
Cerebral blood flow (CBF), 67–68, 67*f*, 67*t*
with inhaled anesthetics, 117–118, 117*f*, 118*f*
nitrodilators and, 509–510
Cerebral cortex. *See* Cerebral hemispheres
Cerebral edema, 68, 787
Cerebral hemispheres, 60–62
anatomy of, 60–61, 60*f*
awareness and recall during anesthesia, 62
dominant *vs.* nondominant, 61
memory, 61–62
Cerebral metabolic oxygen requirements, with inhaled anesthetics, 119
Cerebral protection
with calcium channel blockers, 493
with inhaled anesthetics, 119
Cerebral vasospasm, calcium channel blockers preventing, 493
Cerebrospinal fluid (CSF), 70–72

blood-brain barrier, 72
circulation of, 70–71, 71*f*
formation of, 70
hydrocephalus, 71
inhaled anesthetics and, 119
intracranial pressure, 71
opioids and, 215, 216*f*
papilledema, 71–72
reabsorption of, 70
Chaste tree berries, 749*t*
Chemoreceptors
in elderly patients, 927
reflexes, 369–370
in respiratory control, 583*f*, 584
Chemotherapeutic drugs, 827–851
alkylating agents, 829*t*, 830*t*–831*t*, 836–839
antimetabolites, 829*t*, 831*t*–832*t*, 840–842
antitumor antibiotics, 829*t*, 833*t*, 842–845
cell cycle specificity of, 827, 828*f*
classification of, 828–829, 829*t*–836*t*
corticosteroids used in combination with, 789
platinating drugs, 839
resistance to, 828
signal transduction modulators, 829*t*, 834*t*–835*t*, 847–848
targeted therapies, 835*t*–836*t*, 848–851, 850*t*, 851*t*
topoisomerase inhibitors, 829*t*, 832*t*–833*t*, 842–845, 843*f*, 844*f*, 845*t*
toxicities to, 830*t*–836*t*, 836
tubulin-binding drugs, 829*t*, 845–846
Chest wall rigidity, opioids and, 212
Chief cells, 691
Chills, 88–89
Chimeric antigen receptor T cells, 849–851
Chirality, 42–45
Chloride, in ion channels, 55
Cholecystokinin, 53*t*
Cholesterol, 686, 701–702, 701*f*, 702*t*
Cholinergic fibers, 81
Cholinesterase inhibitors, 248–249, 248*f*
Chromium, in intravenous fluids, 447
Chronic obstructive pulmonary disease (COPD), 588–590, 589*f*, 597–600
Chronic pain syndromes
cannabinoids for, 881
serotonin-norepinephrine reuptake inhibitors for, 859
tricyclic antidepressants for, 864
Chronic respiratory disease, 588–590, 589*f*
Chylomicrons, 701
Circulatory effects, of inhaled anesthetics, 119–127, 119*f*–126*f*
Circulatory overload, transfusion-associated, 645–646, 646*t*
Cirrhotic cardiomyopathy, 685
Citric acid cycle, 699, 699*f*
Clearance, 28

Clonus, 76
Closing capacity (CC), 567–568, 568*f*, 569*f*
Closing volume (CV), 567–568, 568*f*, 569*f*
 C_m . *See* Minimum effective concentration
CNS. *See* Central nervous system
 CO_2 . *See* Carbon dioxide
Coagulation
in elderly patients, 927–928
endothelial regulation of, 629*f*, 631–632, 632*t*
GABA agonists and, 156
inflammation and, 632
initiation of, 627–629, 628*f*, 629*f*, 630*t*
laboratory evaluation of, 660–661
perioperative changes in, 633–634
propagation of, 629–631, 630*f*
testing of, 632–633
Coagulation factors, 630*t*, 704
Cobalamin, 740*t*, 741*f*, 743
Cochlea, 74, 74*f*
Coefficients, 31
Coenzyme Q10, 750*t*
COHb. *See* Carboxyhemoglobin
Collagen diseases, 788
Colloids, 434, 435*t*
albumin, 435*t*
semisynthetic, 434–438, 435*t*, 436*t*, 437*t*, 438*t*
Colon, 694–695, 695*f*
Compartmental models of pharmacokinetics, 26–27, 28*f*
multicompartment, 30–32, 30*f*, 31*f*
one-compartment, 27–30, 28*f*
Competitive antagonism, 12, 13*f*, 314
Complex regional pain syndromes (CRPS), 202–203, 251
Compliance of respiratory system, 568–570, 570*f*, 571*f*
Computed tomography (CT), 66–67
COMT. *See* Catechol-*O*-methyltransferase
COMT inhibitors. *See* Catechol-*O*-methyltransferase inhibitors
Concentration, 17
response relationships *vs.*, 38–40, 40*f*
Concentration effect, of inhaled anesthetics, 101–102, 101*f*
Conduction, 87
Conduction system, of elderly patients, 923–924
Congestive heart failure, β -adrenergic receptor antagonists for, 486
Congestive hepatopathy, 685
Conjugate movement of eyes, 74
Conjugation, 18
Conopeptides, 250–251
Context-sensitive half-time, 36–38, 40*f*
of inhaled anesthetics, 109–110, 109*f*
of opioid agonists, 220–221, 221*f*, 224, 225, 227
Continuous peripheral nerve blocks, with local anesthetics, 291, 291*t*
Continuous positive airway pressure (CPAP), 568

Contraceptives, oral, 796–797
Contraction, 312
Contrecoup, 70
Convection, 87
COPD. *See* Chronic obstructive pulmonary disease
Copper, in intravenous fluids, 447
Cornea, 72*f*
Coronary arteries, 389–390, 390*f*
Coronary artery bypass graft (CABG), 603
Coronary blood flow, with inhaled anesthetics, 123–124
Coronary circulation, 389–390, 390*f*
Coronary steal syndrome, 124
Coronary veins, 390
Coronavirus disease, 821–822
Corpus callosum, 60*f*, 61, 71*f*
Cortical blindness, 73
Corticosteroids, 264, 265*t*, 783–791
for airway, 598–599, 598*t*
clinical uses of, 786–789
mechanism of actions of, 783
pharmacokinetics of, 784–785
for PONV, 709*t*, 712
side effects of, 789–791, 790*f*
synthesis inhibition, 791
synthetic, 784*t*, 785–786
Corticosterone, 760, 760*t*, 783, 784*f*
Corticotropin, 754*t*
Cortisol, 760–762, 760*t*, 783, 784–785, 784*f*, 784*t*
Cortisone, 760*t*, 783, 784*f*, 784*t*
Coughing provocation, with opioids, 213
Cough suppression, with opioids, 211
COX. *See* Cyclooxygenase
COX-1. *See* Cyclooxygenase-1
COX-2. *See* Cyclooxygenase-2
Coxibs, 257–258
CPAP. *See* Continuous positive airway pressure
CPB. *See* Cardiopulmonary bypass
Cranberry, 749*t*
Critical closing pressure, 367
Cross-sensitivity, of local anesthetics, 282
CRPS. *See* Complex regional pain syndromes
Cryoprecipitate, 637, 638*t*, 641
Crystalloids, 431–434, 433*t*
CSF. *See* Cerebrospinal fluid
CT. *See* Computed tomography
Cushing reflex, 370
Cutaneous blood flow, 89
opioids and, 213
Cutaneous disorders, corticosteroids for, 788
Cutaneous vasoconstriction, 89
CV. *See* Closing volume

CVP. *See* Central venous pressure
Cyanide toxicity, 510, 939, 942
Cyanocobalamin (cobalamin, vitamin B₁₂), 740*t*, 741*f*, 743
Cyclic adenosine monophosphate (cAMP), 54, 54*f*
Cyclooxygenase (COX)
inhibitors of, 251–252
lungs and, 610
pathway for, 257, 258*f*
Cyclooxygenase 1 (COX-1), 257–258, 258*f*
Cyclooxygenase 2 (COX-2), 257–258, 258*f*
inhibitors of, 257–258
Cytochrome P450 monooxygenase enzyme systems, 608
Cytoplasm, 10–11
Cytoprotection, 496

D

Damage control resuscitation, 681
Dead space, 576–578, 577*f*, 578*f*
Deafness, 75
Decerebrate rigidity, 76
Decerebration, MAC and, 110, 110*f*
Dehydration, 4
Delirium, emergence, 182–183, 183*f*
Dementia, acetylcholinesterase inhibitors for, 877–878
Dendrites, 49, 76
Dendritic spine, 53*f*
Denervation hypersensitivity, 86
Denosumab, 444
Dependence, with benzodiazepines, 163
Depolarization, 51, 51*f*, 57, 58
Depolarizing neuromuscular block, 314–318
pharmacology of, 315
Dermatome, 65, 66*f*
Descending facilitation pathway, 200–201, 200*f*
Descending inhibition pathway, 200–201, 200*f*
Desoxycorticosterone, 759, 760*t*, 783, 784*f*
Desynchronized sleep, 63
Diabetes insipidus, 793–794
Diabetes mellitus, 769, 770*t*
Diabetic autonomic neuropathy, 85
Diarrhea, enteral nutrition and, 737
Diastolic depolarization, 404
Dibucaine number, 279, 316*t*
Dietary supplements, 748–750, 749*t*, 750*t*
Differential conduction blockade, 276
Diffusion, 6, 7*f*, 7*t*, 379
Diffusion hypoxia, of inhaled anesthetics, 110
Dihydropyridine receptor (DHPR), 310, 311*f*
Dihydropyridines, 491–493, 506–507
Dilutional acidosis, 623, 623*t*

Dilutional coagulopathy, 677
Dipeptidyl-peptidase-4 inhibitors (DPP-4), 773*t*, 776–777
Direct thrombin inhibitors, 663–664, 664*t*
Disinfectant prophylaxis, 821–824
Disseminated intravascular coagulation (DIC), 634
Dissociative anesthesia, 156
Distribution, 15–16, 16*f*
of local anesthetics, 277, 277*f*
Diuretics
aldosterone antagonists, 537*t*, 541–542
aquaporin modulators, 537*t*, 543
carbonic anhydrase inhibitors, 535–536, 536*f*, 537*t*
dopamine receptor agonists, 537*t*, 542
hypokalemia with, 444
lithium and, 879–880, 880*t*
loop, 536*f*, 537*t*
natriuretic peptides, 537*t*, 542
osmotic, 536*f*, 537*t*, 540–541
potassium-sparing, 512, 536*f*, 537*t*, 541
thiazide, 536*f*, 537*t*, 539–540, 880*t*
as vasodilators, 512
vasopressin receptor antagonists, 536*f*, 537*t*, 542–543
DNA, 9–10, 10*f*
Dong quai, 749*t*
Dopamine, 452*f*, 454–456
biochemistry of, 81–82
clinical uses of, 455
G protein-coupled receptors and, 54
as neurotransmitter, 53, 53*t*
renal-dose, 455–456
side effects of, 456
synthetic agonists of, 352–353
Dopamine and serotonin antagonist drugs, 873–875
Dopamine blockers, 728–729, 729*f*
Dopamine norepinephrine multimodal drugs, 868
Dopamine receptor agonists, 537*t*, 542, 869
Dopamine receptor antagonists, 869–873, 870*t*, 880*t*
for PONV, 709*t*, 712–713
Dopamine reuptake inhibitors, 869
Dopaminergic drugs, 868–875
Dorsal horn, in pain, 197–199, 198*f*
Dorsal-lemniscal system, 76
Dose calculations
bolus dosing, 33–35, 34*f*, 35*t*
maintenance infusion rate, 35–36, 37*f*, 38*f*, 39*f*
DPP-4. *See* Dipeptidyl-peptidase-4 inhibitors
Drug interactions, 41–42, 42*f*, 43*f*, 44*f*, 46
with antacids, 719
with antipsychotic drugs, 873
with benzodiazepines, 163
with calcium channel blockers, 494–496, 495*f*, 495*t*

with cardiac glycosides, 464
with dietary supplements, 748–750, 749*t*, 750*t*
with H₂-receptor antagonists, 725–727, 725*t*, 726*f*, 727*f*
with insulin replacement, 772
with levodopa, 351–352
with lithium, 879–880, 880*t*
with MAO inhibitors, 863
with methylxanthines, 355–356
with non- γ -aminobutyric acid sedative-hypnotics, 183
with NSAIDs, 262
with opioid agonists, 223
with opioids, 213
with tricyclic antidepressants, 866
Drug therapy, inhaled anesthetics and, 125
Dysmetria, 64

E

Ear
inner, 74–75, 74*f*
outer, 74, 74*f*
Eardrum, 74*f*, 75
Echinacea, 749*t*
Echocardiography, for cardiac output, 375
Ectopic pacemaker, 405
Edema, 379–380
cerebral, 68, 787
postintubation laryngeal, 788
pulmonary, 385
Effective dose (ED), 41, 41*f*
Efferent nerve fibers, 49
Efficacy, 40–41, 41*f*
Eicosanoids, 610
Elderly patients, 46
antimicrobials and, 812
autonomic nervous system dysfunction and, 84–85
blood:gas partition coefficients in, 1205*f*
cardiovascular system of, 921–924, 922*f*, 923*t*
gas exchange in, 588
gastrointestinal function in, 928–929, 929*t*
renal function in, 929
respiratory system of, 924–927, 925*t*, 926*f*
skeletal muscles in, 930*t*
thermoregulation in, 928, 928*t*
Electrical alternans, 364
Electrocardiogram (ECG), 391
axis for, 392, 392*f*
leads for, 391–392, 391*f*, 392*f*, 392*t*
lead systems for, 392–394, 393*f*
normal deflections of, 394–395, 394*f*
P-R interval, 394, 394*f*

P wave, 394
QRS complex, 395
QT interval, 395
Q wave, 394–395
recording of, 394
ST segment, 395, 395*f*
T wave, 395
U wave, 395
Electroencephalogram (EEG), 68–70
benzodiazepines and, 163
brain wave classification for, 68–69, 68*f*
brain wave monitoring with, 69
clinical uses for, 69
epilepsy, 69
evoked potentials, 69–70
GABA agonists and, 159
inhaled anesthetics and, 116–117
non- γ -aminobutyric acid sedative-hypnotics and, 180–181
opioid agonists and, 222–223
opioids and, 211–212
Electromyography (EMG), 327, 328*f*
Elimination half-time
of benzodiazepines, 168–169
of opioid agonists, 217–219, 218*f*, 220, 224, 225, 227
Emergence delirium, 182–183, 183*f*
Emetic center, 75–76, 75*f*
EMLA. *See* Eutectic mixture of local anesthetics
Enantiomerism, 42–44
Encephalopathy, 743
Endocrine effects
of antipsychotic drugs, 872–873
of dopamine, 456
of levodopa, 351
of lithium, 879
Endocytosis, 6–7, 7*f*
Endoplasmic reticulum, 10
Endorphins
G protein-coupled receptors and, 55
as neurotransmitter, 53*t*
Endothelial function
in coagulation, 629*f*, 631–632, 632*t*
of elderly patients, 923
in pulmonary circulation, 382–383
in systemic circulation, 359, 360*t*
Endothelin (ET-1), 383
Endotheliopathy, 675
Endplate potential, 308
Enkephalins, 208
Enteral nutrition, 735–737
Environmental impact, of inhaled anesthetics, 139–140, 140*t*
Enzyme induction, with barbiturates, 176

Enzyme-linked transmembrane receptors, 53
Enzymes
activity of, 46
phase I, 17–18
phase II, 18
Ephedra, 750
Epidural anesthesia, with local anesthetics, 292–293, 292*f*
Epidural hematoma, 662
Epiglottis, 554–555, 555*f*
Epilepsy, 69, 337, 338*t*
maternal, 343
Epinephrine, 450–453, 452*f*
in cardiopulmonary resuscitation, 939–940, 939*f*
clinical uses of, 450
with inhaled anesthetics, 122, 123*f*
as neurotransmitter, 53*t*
side effects of, 450–453, 453*f*
storage and release of, 86
synthesis of, 86
Epipodophyllotoxins, 832*t*–833*t*
Equal pressure point (EPP), 572–573, 572*f*, 573*f*
Equilibrium, 74, 74*f*
Esophageal varices, 794
Esophagus, 689–690, 689*f*
Estradiol, 795*f*
Estriol, 795*f*
Estrogens, 763, 795–796, 795*f*, 847
Estrone, 795*f*
ET-1. *See* Endothelin
Ethyleneimine, 830*t*
Eustachian tube, 75
Eutectic mixture of local anesthetics (EMLA), 289–290
Evaporative heat loss, 87
Evening primrose, 749*t*
Evoked potentials, 69–70
auditory, 70
with inhaled anesthetics, 117
motor, 70
somatosensory, 69–70
visual, 70
Excitation-contraction coupling, 488
in cardiac muscles, 396
in skeletal muscles, 310–313, 311*f*, 312*f*
Excitatory ligand-gated ion channels, 56–57
Exercise, gas exchange and, 587
Exocytosis, 6–7, 7*f*
Expiration, 563–564
Explicit memory, 62
Exponents, 31
Extracellular fluid, 1, 2, 2*f*, 3*f*
regulation of, 420–421

Extracorporeal ventilatory support, 591
Extraction ratio, 20–22, 21*f*
Extrapulmonary shunt, 577*f*, 578, 578*f*
Extrapyramidal tracts, 64–65, 65*f*
Eyes. *See also* Vision
innervation of, 74
muscular control of, 73–74

F

Facilitated conduction, 87
Factor II, 644
Factor V, 629, 630*t*
Factor VII, 628, 629, 630*t*, 644
Factor VIIa, 654–655
Factor VIII, 628, 629, 630, 630*t*, 640, 641, 645
Factor IX, 628, 630, 630*t*, 644
Factor X, 628, 629, 630, 630*t*, 644
Factor Xa inhibitors, 665*t*, 666–667
Factor XI, 628, 629, 630, 630*t*
Factor XIII, 630–631, 630*t*, 655
Familial hypercholesterolemia, 545
Fat-soluble vitamins, 740*t*, 745–748, 745*f*
Fatty acid deficiency, with TPN, 738
Fatty acid degradation, 702, 702*f*
Fatty acid mobilization, 761
Fetal heart rate monitoring, 912
Fetal neurophysiology, 915–916, 915*f*, 916*t*
Fetal physiology, 913–915
anesthetic toxicity, 914–915
circulation, 910*f*, 913
drug transfer, 913–914
liver function and drug metabolism, 914
Fever, 88
Feverfew, 749*t*
Fibrates, 546*f*, 547*t*, 549–550
Fibrinogen, in clot formation, 630–631, 630*f*
Fibrinogen concentrates, 644
Fibrinolysis, 657*f*, 677
Fibrin tissue adhesives, 656
Fick method, 374, 374*f*
Field of vision, 73
First-order processes, 25–26, 26*f*
First-pass hepatic effect, 25
Fluid responsiveness, 438–439, 439*f*
Fluoride-induced nephrotoxicity, with inhaled anesthetics, 134–136, 135*f*, 136*f*
Folate analogues, 831*t*, 840
Folic acid, 740*t*, 741*f*, 743–744
Follicle-stimulating hormone (FSH), 754*t*, 756
Fovea, 72*f*, 73
Frank-Starling curves, 372–373, 372*f*

Frequency of breathing, with inhaled anesthetics, 127
Fresh frozen plasma (FFP), 636, 638*t*, 639–641
cryoprecipitate, 637, 638*t*, 641
for massive transfusion coagulopathy, 678*f*, 679–680, 679*f*
solvent/detergent-treated, 640–641
Frontal cortex, 60, 60*f*
Functional residual capacity (FRC), 564
obesity and, 586

G

Garlic, 749*t*, 750
Gas exchange, 553
abnormal breathing patterns, 584
altered physiologic conditions and age, 587–588
anesthesia, 584–585
barometric pressure, 587
chronic respiratory disease, 588–590, 589*f*
exercise, 587
extracorporeal ventilatory support, 591
obesity, 586, 586*f*
one-lung ventilation, 590–591
position, 585
sleep-disordered, 586–587
alveolar-arterial oxygen difference, 579
carbon dioxide transport, 581–583, 582*f*
dead space in, 576–578, 577*f*, 578*f*
functional anatomy of
closing capacity and closing volume, 567–568, 568*f*, 569*f*
compliance, 568–570, 570*f*, 571*f*
lower airway, 556–564, 557*f*–562*f*
lung volumes and spiroometry, 564–567, 565*f*, 565*t*, 566*f*
mechanical function, 564, 564*f*, 565*f*
resistance, 570–573, 571*f*
respiratory fatigue, 574
upper airway and gas flow, 553–556, 554*f*–556*f*
work of breathing, 573–574
hypoxic pulmonary vasoconstriction, 383–384, 384*f*, 579–580, 579*f*
oxygen transport, 580–581, 580*f*, 581*f*
oxyhemoglobin dissociation curve, 581, 581*f*
perfusion distribution, 574–575, 575*f*
ventilation matching with, 575, 576*f*, 577*f*, 578
pulmonary circulation and, 574
pulmonary hemodynamics and, 574
respiratory control, 583–584, 583*f*
shunt in, 577*f*, 578–579, 578*f*
ventilation distribution, 574
perfusion matching with, 575, 576*f*, 577*f*, 578
Gastric antral cells, 691
Gastric fluid volume, preoperative decrease in, 729–730, 730*t*
Gastric secretions, 691

Gastrin, 53*t*
Gastroesophageal reflux disease (GERD), 690, 929, 929*t*
Gastrointestinal motility drugs, 717–731
antacids, 717–719
gastrointestinal prokinetics, 728–731, 729*f*, 730*t*, 731*f*
 H_1 -receptor antagonists, 719–722, 719*t*, 720*f*
 H_2 -receptor antagonists, 722–727, 722*f*, 723*t*–725*t*, 726*f*, 727*f*
proton pump inhibitors, 727–728, 727*t*, 728*f*
Gastrointestinal prokinetics, 728–731, 729*f*, 730*t*, 731*f*
Gastrointestinal tract, 687–695, 687*f*, 687*t*
anatomy of, 687
antimicrobials and, 811*t*
blood flow in, 688
colon, 694–695, 695*f*
dopamine and, 456
in elderly patients, 928–929, 929*t*
epinephrine and, 453
esophagus in, 689–690, 689*f*
gastric fluid volume and emptying, 692–693, 692*f*
innervation of, 688–689
levodopa and, 350
maternal, 909
motility of, 689
NSAIDs and, 258, 259
opioids and, 212
pancreas, 695
portal venous pressure in, 688
salivary glands, 689
small intestine, 693–694, 694*t*
splenic circulation, 688
stomach, 690–691, 691*f*
Gate theory for pain, 199, 199*f*
G cells, 691
Gender
MAC of inhaled anesthetics and, 112, 112*f*
opioid agonists and, 218
General anesthesia, 150
opioid antagonist and, 232
Generalized seizures, 338*t*
Genetic disorders, 46
Genetic effects, of inhaled anesthetics, 138
Genitourinary system
epinephrine and, 453
opioids and, 213
GERD. *See* Gastroesophageal reflux disease
GH. *See* Growth hormone
Ginger, 749*t*, 750
Ginkgo biloba, 749*t*, 750
Ginseng, 749*t*, 750
Gliflozins, 773*t*, 776
Glomerular capillaries, 416*f*, 419

Glomerular filtrate, 415
Glomerular filtration rate (GFR), 415–416, 416*f*
Glomerulus, 415–416, 416*f*
Glottis, 554–555, 555*f*
Glucagon, 53*t*, 766–767, 766*t*, 767*f*
Glucagon-like peptide-1 receptor agonists, 776
Glucocorticoids, 264, 265*t*, 760–762, 760*t*, 783–784, 791
Gluconeogenesis, 686, 699, 699*f*, 704, 761
Glucosamine, 750*t*
Glucose
energy release from, 699–700, 699*f*
oral regulators for, 772–777, 773*f*, 773*t*, 774*f*, 775*t*
 α -Glucosidase inhibitors, 777
Glue, biologic, 656
Glutamate, 49
in excitatory ligand-gated ion channels, 57
inhaled anesthetics and, 114
inhibition of release of, 251
as neurotransmitter, 53, 53*t*
Glutamate antagonists, 876–877
Glycerol, 700, 700*f*
Glycine
in inhibitory ligand-gated ion channels, 57
as neurotransmitter, 53*t*
Glycocalyx, 376, 376*f*, 377–379, 378*f*
Glycogen, 686, 699
Goldenseal, 749*t*
Golgi apparatus, 11
Gonadotropin-releasing drugs, 835*t*–836*t*
Gonadotropins, 754*t*, 756, 792
G protein-coupled receptors, 53–55, 54*f*
G protein-gated ion channels, 57, 58*f*
Graft versus host disease, with platelet transfusions, 643
Grand mal epilepsy, 69
Granulations, 70
Gray matter, 64, 64*f*
Ground substance, 442
Growth hormone (GH, Somatotropin), 754*t*, 755–756, 755*f*, 755*t*, 792

H

HAE. *See* Hereditary angioedema
Half-time
context-sensitive, 36–38, 40*f*
of inhaled anesthetics, 109–110, 109*f*
of opioid agonists, 220–221, 221*f*, 224, 225, 227
elimination
of benzodiazepines, 168–169
of opioid agonists, 217–219, 218*f*, 220, 224, 225, 227
Halothane hepatitis, 132–133, 132*f*

HCN channels, inhaled anesthetics and. *See* Hyperpolarization-activated cyclic nucleotide-gated channels, inhaled anesthetics and

Head ganglion. *See* Hypothalamus

Hearing, 74–75, 74*f*

Hearing impairment, 75

Heart

- anatomy of, 388–395, 389*f*
- cardiac conduction system, 390–395, 391*f*–395*f*, 392*t*
- coronary circulation, 389–390, 390*f*
- of elderly patients, 921–922, 922*f*, 923*t*
- electrocardiogram axis of, 392, 392*f*

Heart arrest, 936

Heart block, 406, 406*f*, 407*f*

Heart disease

- ischemic, 400–401
- valvular. *See* Valvular heart disease

Heart failure, 401, 402*t*

Heart rate

- fetal monitoring, 912
- inhaled anesthetics and, 120, 120*f*, 121*f*
- variability of, 371

Heat loss, 87

Hematology, maternal, 904–905, 904*t*, 905*t*

Hemodynamic calculations, 399–400, 400*t*

Hemoglobin (Hb), 580–581, 581*f*

Hemoglobin buffering systems, 619

Hemolytic anemia, with antimicrobials, 811*t*

Hemorrhage

- acute, 89
- postpartum, 680–681
- resuscitation and, 938, 941

Hemorrhagic shock, 373, 938, 941

Hemosiderin, 446

Hemostasis, 627–634, 628*f*

- antithrombin and proteins C and S, 632–633
- coagulation
 - endothelial regulation of, 629*f*, 631–632, 632*t*
 - initiation of, 627–629, 628*f*, 629*f*, 630*t*
 - perioperative changes in, 633–634
 - propagation of, 629–631, 630*f*
 - critical factor levels for, 631
 - during massive transfusion coagulopathy, 678
 - perioperative, 656, 657*f*
- Hemostatic therapy, 633

Heparin-induced thrombocytopenia (HIT), 662

Hepatic blood flow, 684, 684*f*

- control of, 685
- with inhaled anesthetics, 131, 131*f*

Hepatic clearance, 18–22, 19*f*, 20*f*, 21*f*

- with inhaled anesthetics, 131

Hepatic function

GABA agonists and, 156
inhaled anesthetics and, 131, 132*f*
nitrodilators and, 509
NSAIDs and, 261
statins and, 548
Hepatic physiology, of neonates, 892
Hepatobiliary complications, with TPN, 738
Hepatocytes, 683, 684*t*
Hepatopathy, congestive, 685
Hepatotoxicity
with antimicrobials, 811*t*
with inhaled anesthetics, 132–134, 132*f*–134*f*
with local anesthetics, 287
Hereditary angioedema (HAE), 645
HES solutions. *See* Hydroxyethyl starch solutions
Hiatal hernia, 690
Hill coefficient, 38
Histamine
G protein-coupled receptors and, 55
in lungs, 609, 610
with neuromuscular-blocking drugs, 321
as neurotransmitter, 53, 53*t*
Histamine receptor antagonists. *See* Antihistamines
HIT. *See* Heparin-induced thrombocytopenia
HIV-infected patients, antimicrobials and, 812–814
HMG-CoA reductase inhibitors, 545–546, 546*f*
Hofmann elimination, 318, 319
Hormonal changes, with opioids, 213
Hormones. *See also* specific hormones
cardiac function control by, 396–397
mechanism of action of, 753
tissue blood flow control by, 368–369
Horner syndrome, 74
HPV. *See* Hypoxic pulmonary vasoconstriction
5-HT. *See* Serotonin
5-HT₃ receptor antagonists, 709–710, 709*t*
Human ether-a-go-go related gene (hERG), 56
Hydrocephalus, 71
Hydrogen ion concentration regulation, 617–621
buffer systems for, 617–619, 618*f*, 618*t*, 619*f*
intracellular pH regulation, 619, 619*t*
renal response to, 620–621, 620*f*
ventilatory response to, 619–620
Hydrolysis, 18
Hydrostatic pressure, 365, 366*f*
3-Hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase) inhibitors, 545–546, 546*f*
Hydroxyapatites, 442
Hydroxyethyl starch (HES) solutions, 434–438, 435*t*, 436*t*, 437*t*, 438*t*
5-Hydroxytryptamine. *See* Serotonin (5-HT)
Hyperalgesia, 196, 227–228, 228*f*
Hypercalcemia, 441–442, 791

nondepolarizing neuromuscular block and, 320

Hypercarbia
morphine and, 215, 216*f*
with TPN, 738

Hypercoagulability, postoperative, 633–634

Hyperglycemia, with TPN, 738

Hyperkalemia, 444–445
with antimicrobials, 812*t*
succinylcholine and, 317

Hyperlipidemia, 545
bile acid resins for, 546*f*, 547*t*, 548–549
fibrates for, 546*f*, 547*t*, 549–550
niacin for, 546*f*, 547*t*, 549
omega-3 fatty acids for, 550
proprotein convertase subtilisin/kexin type 9 for, 546*f*, 547*t*, 548
statins for, 546–548, 546*f*, 547*t*
treatment for, 546–550, 547*t*

Hypermagnesemia, 440

Hyperpolarization-activated cyclic nucleotide-gated (HCN) channels, inhaled anesthetics and, 115

Hypersensitivity reactions, to NSAIDs, 262

Hypertension
β-adrenergic receptor antagonists for, 484
idiopathic intracranial, 535
pulmonary, 385–386, 386*t*
rebound, 504

Hyperthermia, 88, 88*t*. *See also* Malignant hyperthermia

Hyperthyroidism, 486, 779–782, 780*t*

Hypertonic fluids, 4, 4*f*

Hypervitaminosis A, 746

Hypervitaminosis D, 747

Hypnotics, 150. *See also* Sedative-hypnotics
in lungs, 608
maternal use of, 899*t*

Hypocalcemia, 441, 791–792

Hypofibrinogenemia, 677

Hypoglycemia
with insulin replacement, 772
with TPN, 738

Hypokalemia, 444, 445, 452–453

Hypomagnesemia, 440

Hyponatremia, serotonergic drugs and, 857

Hypotension
during anesthesia, 794
antipsychotic drugs and, 872

Hypothalamic-pituitary-adrenal axis, benzodiazepines and, 163

Hypothalamus, 60*f*
histamine and, 55
hormones of, 753–754, 754*t*
limbic system and, 63
in thermoregulation, 87

Hypothermia. *See also* Perioperative hypothermia

acid-base disturbances during, 625, 625*t*
with antipsychotic drugs, 873
massive transfusion coagulopathy and, 677
nondepolarizing neuromuscular block and, 320
Hypothyroidism, 779, 780*t*
Hypotonic fluids, 4, 4*f*
Hypoxemia, inhaled anesthetics and, 129
Hypoxic death, 939
Hypoxia. *See* Diffusion hypoxia
Hypoxic pulmonary vasoconstriction (HPV), 383–384, 384*f*, 579–580, 579*f*, 606–607
Hysteresis, 32–33

I

ICP. *See* Intracranial pressure
ICS, for airway. *See* Inhaled corticosteroids, for airway
Idiopathic intracranial hypertension, 535
Ileus, 689
Immobility, mechanism of, of inhaled anesthetics, 115
Immune checkpoint inhibitors, 849, 850*t*
Immune modulation
in chemotherapy, 836*t*, 849
with dopamine, 456
with opioids, 233–234, 234*f*
transfusion and, 648
Immunonutrition, 739
Immunosuppression, 788
Immunotherapies, cancer, 849, 850*t*, 851*t*
Impaired memory. *See* Postoperative cognitive dysfunction
Impedance cardiography, 375
Incessant ventricular tachycardia, 521
Indicator dilution method, 374
Individual variability, 45–46, 45*t*
Infants. *See also* Neonates
gas exchange in, 587–588
pain in, 204
Infection resistance
of GABA agonists, 157
inhaled anesthetics and, 138
Inflammation
airway and, 597–600, 598*t*
inhaled corticosteroids, 598–599, 598*t*
leukotriene modifiers for, 598*t*, 599
mast cell stabilizers, 598*t*, 599
methylxanthines, 598*t*, 599–600
systemic corticosteroids, 599
coagulation and, 632
transfusion and, 645
Infusion pharmacokinetics, 29–30
Inhaled β_2 -adrenergic receptor agonists, 595–596, 596*t*
Inhaled anesthetics

in adults, 102, 102*f*
bowel segment pressures with, 100, 100*f*
clinically useful, 96–100, 96*t*, 97*f*
comparative pharmacology of, 116–139, 116*t*
bone marrow function, 138–139, 139*f*
central nervous system effects of, 116–119, 117*f*, 118*f*
circulatory effects of, 119–127, 119*f*–126*f*
genetic effects of, 138, 138*f*
hepatic effects of, 131–134, 131*f*–134*f*
infection resistance, 138
obstetric effects of, 137–138, 137*f*
peripheral neuropathy, 139
renal effects of, 134–136, 134*f*–136*f*
skeletal muscle effects of, 136–137, 137*f*
total body oxygen requirements, 139
ventilation effects of, 127–130, 127*f*–131*f*, 128*t*
cost considerations for, 95–96
environmental impact of, 139–140, 140*t*
history of, 95, 96*f*
metabolism of, 139
in neonates, 102
nondepolarizing neuromuscular block and, 320
pharmacodynamics of, 110–116
mechanisms of action, 113–116, 114*f*
minimal alveolar concentration, 110–113, 110*f*, 111*t*, 112*f*, 113*f*
pharmacokinetics of, 97*f*, 100–110
alveolar partial pressure, 101–103, 101*f*–103*f*, 101*t*
alveolar-to-venous partial pressure differences, 107–108, 107*t*
cardiac output, 106–107
recovery from, 99*f*, 108–110, 108*f*, 109*f*
solubility, 103–106, 104*t*, 105*f*, 106*f*
for present and future, 95
Inhaled anticholinergics, 596*t*, 597
Inhaled corticosteroids (ICS), for airway, 598–599
Inhaled partial pressure (PI), of inhaled anesthetics, 101–102, 101*f*, 102*f*
Inhibitory ligand-gated ion channels, 57
Injection pain, with GABA agonists, 158, 160
Inodilators, 465
Inotropes, pulmonary circulation and, 604
Inspiration, 563
Insulin, 764–765, 764*f*, 765*f*, 765*t*
replacement therapy for, 769–770
pharmacokinetics of, 770
preparations and delivery of, 770–771, 771*t*
side effects of, 772
resistance to, 772
Intercalation, 842
Interstitial fluid, 1, 2*f*, 3*f*
pressure of, 379
colloid osmotic, 382, 385
space, 381–382

Intra-arterial injection, of barbiturates, 176
Intracellular fluid, 1, 2, 2*f*, 3*f*
Intracellular pH regulation, 619, 619*t*
Intracranial pressure (ICP), 71
with antimicrobials, 811*t*
barbiturates for, 175, 175*f*
carbonic anhydrase inhibitors and, 535–536
with inhaled anesthetics, 119
non- γ -aminobutyric acid sedative-hypnotics and, 180, 180*f*
with opioid agonists, 223, 223*f*
succinylcholine and, 318
Intragastric pressure, succinylcholine and, 317–318
Intraocular pressure (IOP), 72
dopamine and, 456
GABA agonists and, 156, 156*f*
succinylcholine and, 317
Intraoperative vasoconstriction, 90
Intrapulmonary bronchus, 561*f*
Intrathecal drug administration, neurotoxicity with, 251
Intravascular volume, maternal, 904–905, 904*f*
Intravenous anesthetics, airway and, 600*t*, 601, 601*f*
Intravenous fluids
colloids, 434, 435*t*
albumin, 434, 435*t*
semisynthetic, 434–438, 435*t*, 436*t*, 437*t*, 438*t*
constituents of
calcium, 441–444, 443*f*
chromium, 447
copper, 447
iron, 446–447
magnesium, 439–441
manganese, 448
molybdenum, 448
phosphate, 445–446
potassium, 444–445
selenium, 447–448
zinc, 447
crystalloids, 431–434, 433*t*
fluid responsiveness, 438–439, 439*f*
Intravenous regional anesthesia, 291–292, 292*f*
Intravenous sedation, 150
benzodiazepines for, 166–167
GABA agonists for, 152–153
Intrinsic clearance, 21–22, 21*f*
Intrinsic-PEEP, 590
Inverse agonists, 12, 13*f*, 14, 14*f*
Ion channels, 7–8, 8*f*, 8*t*, 55–57
evaluation of, 52
G protein-gated, 57, 58*f*
ligand-gated, 53, 56–57, 56*f*
excitatory, 56–57

inhaled anesthetics and, 114–115
inhibitory, 57
other, 57
voltage-gated, 55–57
Ionization, 22–24, 23*t*
Ionotropic receptors
glutamate, 57
inhaled anesthetics and, 114–115
ligand-gated ion channels, 55
Ion trapping, 23–24, 24*f*
IOP. *See* Intraocular pressure
Iron
deficiency of, 446–447
in intravenous fluids, 446–447
Ischemic heart disease, 400–401
Ischemic injury, barbiturates for, 175, 175*f*
Ischemic optic neuropathy (ION), 73
Ischemic preconditioning, with inhaled anesthetics, 126–127, 126*f*
Ischemic reflex of CNS, 370
Isotonic solutions, 3, 4*f*

J

Jaundice, 686
obstructive, 873
Jugular venous pressure, 365, 365*f*, 365*t*
Jumping conduction, 50, 50*f*
Junctional paroxysmal tachycardia. *See* Nodal paroxysmal tachycardia
Juxtaglomerular apparatus, 420, 420*f*
Juxtamedullary nephron, 415, 416*f*

K

Kava-kava, 749*t*, 750
Ketogenesis, 704
Kidneys. *See also* Acute kidney injury (AKI)
anatomy of, 415–419, 416*f*, 417*t*, 418*f*
anesthesia and, 426–429
function measurement, 423
Kinemyography, 329, 330*f*
Kola nut, 749*t*
Krebs cycle. *See* Citric acid cycle

L

LABA. *See* Long-acting β -adrenergic agonists, for airway
Lactic acidosis, 622–623, 773–774
with GABA agonists, 156–157
Lamellar bodies, 559, 561*f*
Larynx, 553–555, 554*f*, 555*f*
LAST. *See* Local anesthetic systemic toxicity
Left atrial pressure, 381

Lens, 72, 72*f*
Lethal dose (LD), 41, 41*f*
Leucovorin, 744
Leukemia, corticosteroids used in treatment of, 789
Leukoagglutinins, 646
Leukopenia, with antimicrobials, 811*t*
Leukoreduction, 642–643
Leukotriene modifiers, for airway inflammation, 598*t*, 599
Leukotrienes, 610
LH. *See* Luteinizing hormone
Licorice, 749
Ligand-gated ion channels, 53, 56–57, 56*f*
excitatory, 56–57
inhaled anesthetics and, 114–115
inhibitory, 57
Limbic system, 60*f*, 63
Linear pharmacokinetics, 29
Lipid disorders, 545–546
Lipid metabolism, 686–687, 700*f*–702*f*, 701–702, 701*t*
Lipodystrophy, with insulin replacement, 772
Lipoproteins, 701
classification of, 545, 546*t*
metabolism of, 545, 687
Liposomal local anesthetics, 296, 296*f*
 β -Lipotropin, 754*t*
Lithium, 878–880
dosage and monitoring, 879
drug interactions with, 879–880, 880*t*
mechanism of action of, 878–879
side effects of, 879
toxicity of, 880, 880*t*
Liver, 683–687, 684*f*
anatomy of, 683–684, 684*f*
bile secretion by, 685–686, 686*f*
in elderly patients, 928
fetal, 914
metabolic functions of, 686
reservoir function of, 685
Liver function tests, inhaled anesthetics and, 131, 132*f*
Local anesthetics, 272
adverse effects of, 282–287
allergic reactions, 282
hepatotoxicity, 287
LAST, 282–285, 283*t*, 284*f*, 285*f*, 286*f*
methemoglobinemia, 287
neurotoxicity, 285–287
ventilatory response to hypoxia, 287
airway and, 602
calcium channel blockers and, 494
clearance of, propranolol and, 478, 478*f*
cocaine toxicity, 297–298, 298*f*

liposomal, 296, 296*f*
in lungs, 608
maternal use of, 901*t*
mechanism of action of, 273–275, 275*f*
frequency-dependent blockade, 275
site of action targets, 275
sodium channels, 273–275, 276*f*
metabolism of
amides, 278–279
esters, 279–280
minimum effective concentration for, 275–276
molecular structure of, 272, 273*f*
racemic mixtures or pure isomers, 273
structure-activity relationships of, 272–273, 274*t*
nondepolarizing neuromuscular block and, 320
pharmacokinetics of, 277–281
absorption and distribution, 277, 277*f*
adjuvant mixed with, 280
alkalinization, 280
combinations of, 281
lung extraction, 277
placental transfer of, 278, 278*f*
renal elimination and clearance, 278
vasoconstrictors with, 281, 281*f*
systemic, 264–267
uses of, 287–297
Bier block, 291–292, 292*f*
epidural anesthesia, 292–293, 292*f*
local infiltration, 290
peripheral nerve block anesthesia, 288*t*, 290–291
regional anesthesia, 287–297, 288*t*–289*t*
spinal anesthesia, 293, 294*f*
topical anesthesia, 288*t*–289*t*, 289
tumescent liposuction, 297
Local anesthetic systemic toxicity (LAST), 282–285, 283*t*, 284*f*, 285*f*, 286*f*
Long-acting β -adrenergic agonists (LABA), for airway, 598, 598*t*
Long-term memory, 61–62
Loop diuretics, 536–538, 536*f*, 537*t*
Low-dose dopamine, 455–456
Lower airway
 expiration, 563–564
 inspiration, 563
 pulmonary circulation, 562–563, 562*f*
 respiratory airways and alveoli, 557–562, 560*f*–562*f*
 thorax and respiratory muscles, 563
tracheal and bronchial structure, 556–557, 557*f*, 558*f*, 559*f*
Lumbar disc disease, 787–788
Lungs
 endogenous substances of, 608–610, 609*f*
 exogenous substances of, 608
GABA agonists and, 156

intrinsic pharmacologic effects of, 607–610, 607*f*
local anesthetics and, 277
regional blood flow in, 384, 385*f*
Lung volumes, 564–567, 565*f*, 565*t*, 566*f*
closing capacity and closing volume, 567–568, 568*f*, 569*f*
compliance, 568–570, 570*f*, 571*f*
of elderly patients, 925–927, 926*f*
maternal, 908–909
resistance, 570–573, 571*f*
Luteinizing hormone (LH), 754*t*, 756
Lymphatics, 379–380, 379*f*
pulmonary, 381
Lysosomes, 10–11

M

MAC. *See* Minimal alveolar concentration; Minimum anesthetic concentration
Macrolides, 731, 731*f*, 818–819
Macula densa, 416, 420
Magnesium
in intravenous fluids, 439–441
nondepolarizing neuromuscular block and, 320
plasma concentration of, 423
pulmonary circulation and, 603–604
role of, 440
Magnesium sulfate
airway and, 602
opioids and, 252
Magnetic resonance imaging (MRI), 66–67
Maintenance infusion rate, 35–36, 37*f*, 38*f*, 39*f*
Malignant hyperthermia
with inhaled anesthetics, 137
serotonin syndrome mistaken as, 858*t*
Malnutrition, 734
Manganese, in intravenous fluids, 448
MAO. *See* Monoamine oxidase
MAO-B inhibitors. *See* Monoamine oxidase type B inhibitors
MAO inhibitors. *See* Monoamine oxidase inhibitors
MAP. *See* Mean arterial pressure
Masseter spasm, succinylcholine and, 318
Massive transfusion coagulopathy, 674–681
adverse effects of, 676
bleeding causes in, 677
dilutional coagulopathy for, 677
fibrinolysis for, 677
hemostasis monitoring during, 678
hemostatic changes with, 675
perioperative, 676
hypofibrinogenemia, 677
hypothermia, acidosis and, 677
protocols for, 676, 678*f*, 679*f*

RBCs and anemia in, 676
therapeutic approaches to, 675
treatment for, 678–680, 678*f*, 679*f*
Mass reflex, 368
Mast cell stabilizers, for airway inflammation, 598*t*, 599
Maternal epilepsy, 343
Maternal physiology
cardiovascular, 894–906, 904*t*
gastrointestinal changes, 909
inhaled anesthetics during delivery, 137–138
MAC of inhaled anesthetics, 112
neurologic changes, 904*t*, 909–910
during pregnancy and delivery, 894, 904*t*
pulmonary changes, 904*t*, 906–909, 907*f*, 907*t*, 908*f*
renal changes, 904*t*, 909, 910*f*
Mean arterial pressure (MAP)
during and after cardiopulmonary bypass, 363, 363*f*
with inhaled anesthetics, 119–120, 119*f*, 120*f*
Mechanical ventilation, spontaneous ventilation vs., 102–103, 103*f*
Mechanism of immobility, of inhaled anesthetics, 115
Mechanisms of action
of ACE inhibitors, 505
of acetylcholinesterase inhibitors, 322
of α -adrenergic receptor agonists, 473, 503–504, 503*f*
of α -adrenergic receptor antagonists, 471
of β -adrenergic receptor antagonists, 474, 501–502
of antiarrhythmic drugs, 516–517, 517*f*
of antiepileptic drugs, 338–342
of antipsychotic drugs, 869
of barbiturates, 173
of benzodiazepines, 162–163, 162*f*
of calcium channel blockers, 487–488, 490*f*
of cardiac glycosides, 462–463, 463*f*
of chemotherapeutic drugs, 829*t*
of corticosteroids, 783
of GABA agonists, 151, 158
of gastrointestinal prokinetics, 729
of H₂-receptor antagonists, 722, 723*t*
of hormones, 753
of inhaled anesthetics, 113–116
mechanism of immobility, 115
Meyer-Overton theory, 113
potential mediators of, 114–115
stereoselectivity, 114, 114*f*
unconsciousness, 115–116
of lithium, 878–879
of local anesthetics, 273–275, 275*f*
frequency-dependent blockade, 275
site of action targets, 275
sodium channels, 273–275, 276*f*
of MAO inhibitors, 862

of methylxanthines, 355
of nitrodilators, 508–509, 511
non- γ -aminobutyric acid sedative-hypnotics, 176–177
of oral glucose regulators, 773, 774
of serotonergic drugs, 855
of tricyclic antidepressants, 864
of warfarin, 665
Mechanomyography (MMG), 327, 328*f*
Medulla, 60*f*. *See also* Brainstem
Medullary respiratory centers
chemoreceptors in, 583*f*, 584
neural connections to, 584
Megaloblastic anemia, 743
Meglitinides, 777
Melatonin, 750*t*, 792–793, 793*f*
Memory, 61–62
Memory engram, 62
Memory trace, 62
Menopause, 763
Menstruation, 763
Mental function, with inhaled anesthetics, 117
MEPP. *See* Miniature endplate potential
Metabolic acidosis, 621*t*, 622–624, 624*t*, 625
with GABA agonists, 156–157
with TPN, 738
Metabolic alkalosis, 621*t*, 624, 625
Metabolic effects, of epinephrine, 452
Metabolic syndrome, 705, 705*t*
Metabolism, 17, 697–706
of acetylcholine, 83–84
of β -adrenergic receptor antagonists, 477–478, 482
of antiepileptic drugs, 338
of antipsychotic drugs, 870
of benzodiazepines, 165, 165*f*, 168, 168*f*
carbohydrates, 686, 697–700, 699*f*
of desflurane, 98
fetal, 914
of GABA agonists, 158–159
of levodopa, 350
lipids, 686–687, 700*f*–702*f*, 701–702, 701*t*
of lipoproteins, 545
of local anesthetics
amides, 278–279
esters, 279–280
of nitrodilators, 509
of non- γ -aminobutyric acid sedative-hypnotics, 178, 178*f*
of norepinephrine, 82
of opioid agonists, 216–217, 217*f*, 218, 220, 224, 225, 226–227
pathways of, 17–18
proteins, 687, 702–704, 702*t*, 703*f*, 703*t*
rate of, 18–22, 19*f*

of selective relaxant binding agents, 323
of sevoflurane, 99, 100*f*
stress and, 704–706

Metabotropic receptors
glutamate, 57
G protein-coupled receptors and, 55
inhaled anesthetics and, 114–115

Metarterioles, 375, 376*f*

Methemoglobinemia
with local anesthetics, 287
with nitrodilators, 511

Methylxanthines, 355–356
for airway inflammation, 598*t*, 599–600
Meyer-Overton theory, of inhaled anesthetics, 113

Michaelis constant, 19, 20*f*

Microcirculation, 375–379
anatomy of, 375–377, 376*f*, 376*t*, 377*t*
blood flow, 377
capillary endothelium, 377–379
fluid movement across capillary lumen and interstitium, 377–379

Milk-alkali syndrome, 718

Mineralocorticoids, 759–760, 760*t*

Miniature endplate potential (MEPP), 308

Minimal alveolar concentration (MAC)
of inhaled anesthetics, 96, 110–113, 110*f*, 111*t*
aging and, 112
factors that alter, 111–113, 111*t*, 112*f*, 113*f*
gender and, 112, 112*f*
maternal, 904*t*, 909–910

Minimum anesthetic concentration (MAC), 62

Minimum effective concentration (C_m), for local anesthetics, 275–276

Minute ventilation, maternal, 907–908, 908*f*

Mitochondria, 10

Mitral regurgitation, 403, 404*f*

Mitral stenosis, 402–403

Mitral valves, 389, 389*f*

MMG. *See* Mechanomyography

Molybdenum, in intravenous fluids, 448

Monoamine oxidase (MAO), 82, 861–862, 862*f*

Monoamine oxidase (MAO) inhibitors, 856*t*, 861–864
anesthesia and, 863–864
antimicrobials and, 812*t*
and autonomic nervous system, 80*t*
dietary restrictions with, 861*t*, 862–863
drug interactions with, 863
levodopa and, 351
mechanism of action, 862
overdose of, 863
side effects of, 862
tricyclic antidepressants and, 866

Monoamine oxidase type B (MAO-B) inhibitors, for Parkinson disease, 353

Monoaminergic receptors, 177
Monoclonal antibodies, 834*t*–835*t*, 848
Motion-induced nausea, prevention of, 711
Motor cortex, 60, 60*f*
Motor evoked potentials, 70
Motor impulses, pathways for peripheral, 76
Motor nerve, 310
MRI. *See* Magnetic resonance imaging
Multicompartment models, 30–32, 30*f*, 31*f*
Multimodal resuscitation, 681
Multiple sclerosis, 251
Muscarinic receptors, 54*f*, 56, 57, 177
Muscle impulse, 52
Muscle relaxants
centrally acting, 356–357
maternal use of, 900*t*
Myalgias
with antimicrobials, 812*t*
succinylcholine and, 318
Myasthenia gravis, 788
Myelin, 49–50, 50*f*
Myocardial depression. *See* Cardiovascular depression
Myocardial ischemia, β -adrenergic receptor antagonists for, 485
Myocardium, 395–397, 396*f*
performance of, 398–399, 398*f*, 399*f*
Myoclonus, with GABA agonists, 160–161
Myoglobinuria, succinylcholine and, 317
Myotome, 65

N

nAChR. *See* Nicotinic acetylcholine receptors
NANC system. *See* Nonadrenergic noncholinergic system
Narcotics, 206
Nasal administration, 25
Nasal field of vision, 73
Nasopharynx, anatomy of, 553, 554*f*
Natriuretic peptides, 537*t*, 542
Nausea, 75–76, 75*f*. *See also* Postoperative nausea and vomiting (PONV)
motion-induced, prevention of, 711
opioids and, 212–213
with PCA, 250
Neonates
blood:gas partition coefficients in, 105, 105*f*
gas exchange in, 587–588
inhaled anesthetics in, 102
morbidity of, neuraxial opioids and, 237
NSAIDs and, 262
pain in, 204
physiology of, 889–892
cardiovascular, 889–890, 890*f*

fluid, electrolyte, and renal, 891–892
hepatic, 892
neurophysiology, 892
respiratory, 890–891, 891*t*
thermoregulation by, 891
Nephrogenic diabetes insipidus (NDI), 543
Nephron, 415, 416*f*
Nephrotoxicity. *See also* Fluoride-induced nephrotoxicity, with inhaled anesthetics with antimicrobials, 811*t*, 818
Nerve fibers, 49, 76
afferent, 49–50, 50*t*
efferent, 49
Nerve impulse, 52
Neural control, of cardiac function, 396, 396*f*
Neuraxial analgesia, 179
Neuraxial opioids, 235–238
pharmacokinetics of, 235–236
side effects of, 236–238, 237*f*
Neurocirculatory responses, of inhaled anesthetics, 124, 124*f*, 125*f*
Neurogenic shock, 373
Neurokinin-1 antagonists, for PONV, 709*t*, 713–714
Neurokinin A (NKA), 595
Neuroleptic malignant syndrome, 858*t*, 871
Neuromodulators, 52–53
Neuromuscular blockade
acetylcholinesterase inhibitors and, 322–323
with antimicrobials, 811*t*
clinical considerations for, 329–330, 331*f*
duration of, 316, 316*t*
objective (quantitative) evaluation of, 327–329, 328*f*, 329*f*
subjective (qualitative) evaluation of, 326–327, 326*f*, 327*f*
Neuromuscular-blocking drugs, 314
action at NMJ, 314
adverse effects of, 320–321
allergic reactions with, 321
autonomic effects, 321
histamine release, 321
awareness and, 62
calcium channel blockers and, 494, 495*f*
depolarizing, 314–318
pharmacology of, 315
lithium and, 880*t*
neuromuscular function monitoring after, 326
nondepolarizing, 314–315, 315*t*
pharmacology of, 318–319
potency of, 319–320
pulmonary circulation and, 603
reversal of, acetylcholinesterase, 322–323
structure of, 314
Neuromuscular junction (NMJ), 305–310, 307*f*
inhaled anesthetics and, 136–137, 137*f*, 320

nAChR at, 308–310, 309*f*
neuromuscular-blocking drugs at, 314
synaptic cleft of, 306, 308, 308*f*
synaptic vesicles of, 307–308, 307*f*
Neuromuscular transmission, 310–313, 311*f*, 312*f*
Neuronal nicotinic acetylcholine receptors, 177
Neuronal (N-type) voltage-gated calcium channels, 250
Neurons, 49. *See also* Neurotransmitter; Receptors; Synapses
action potential of, 49, 51–52
abnormal, 52
elements of, 51*f*
ion channel evaluation, 52
propagation of, 52
peripheral, 50–51
posttetanic facilitation, 59
pseudounipolar, 76
responsiveness of, 59
Neuropathic pain, 202
Neurophysiology
of aging, 930–931
of neonates, 892
Neurotensin receptor type 1 (NTR1), 251
Neurotoxicity
with inhaled anesthetics, 130
with intrathecal drug administration, 251
with local anesthetics, 285–287
Neurotransmitter, 49, 52–53, 53*f*
receptor interactions with, 53*f*, 80*t*, 82, 83
Neutropenia, with antimicrobials, 811*t*
Neutrophils, transfusion and, 648
Niacin. *See* Nicotinic acid
Nicotinic acetylcholine receptors (nAChR), 56–57, 58, 81, 86
at NMJ, 308–310, 309*f*
Nicotinic acid (niacin, vitamin B₃), 546*f*, 547*t*, 549, 740*t*, 741*f*, 742
Nitric oxide (NO), 382–383, 507–508, 508*f*
airway and, 595
pulmonary circulation and, 604–605, 605*f*
Nitrodilators, 508–512
Nitrogen mustards, 830*t*, 837–838
Nitrosoureas, 830*t*, 838–839
NKA. *See* Neurokinin A
N-methyl-D-aspartate (NMDA) receptors, 177, 177*f*, 249–250
NMJ. *See* Neuromuscular junction
Nociception, 195
dorsal horn for, 197–199, 198*f*
supraspinal modulation of, 200
Nociceptors, 195–196, 197*f*
Nodal paroxysmal tachycardia, 409
Nonadrenergic noncholinergic (NANC) system, 595
Noncatecholamines, synthetic, 451*t*, 458–460, 458*f*–460*f*, 460*t*
Noncompetitive antagonism, 12, 13*f*

Nondepolarizing neuromuscular block, 314–315, 315*t*
pharmacology of, 318–319
benzylisoquinolinium compounds, 318–319
steroidal compounds, 319
potency of, 319–320
Nonhemorrhagic hypovolemic shock, 373
Nonshivering thermogenesis, 87–88
Nonsteroidal antiinflammatory drugs (NSAIDs), 257
characteristics of, 258, 260*t*–261*t*
coxibs, 257–258
COX pathway for, 257, 258*f*
gastrointestinal absorption of, 258, 259
hyperkalemia with, 445
lithium and, 880*t*
overdose of, 263–264, 263*t*
side effects of, 259–262
Non- γ -aminobutyric acid sedative-hypnotics, 176–185, 177*f*, 178*f*, 180*f*, 181*t*, 183*f*–185*f*
Noradrenergic agents, 864–868
Norepinephrine, 452*f*, 453–454
aging and, 924
clinical uses of, 454
G protein-coupled receptors and, 54
with inhaled anesthetics, 124*f*
as neurotransmitter, 53, 53*t*, 81–82
receptors for, 82
side effects of, 454
storage and release of, 82, 86
synthesis of, 81–82, 84*f*, 86
termination of action of, 82
Norepinephrine agonists, 867–868
Norepinephrine and serotonin multimodal drugs, 856*t*, 860–861
Norepinephrine dopamine reuptake inhibitors, 868
Norepinephrine reuptake inhibitors, 864–868
Normocytic normochromic anemia, with antimicrobials, 811*t*
Nosocomial infections, 810–812
NTR1. *See* Neuropeptid Y receptor type 1
N-type voltage-gated calcium channels. *See* Neuronal voltage-gated calcium channels
Nucleoside transporter systems, benzodiazepines and, 163
Nucleus, 9–10, 9*f*
Nutrition, 733–750
enteral, 735–737
parenteral, 737–739, 738*t*
support, 734–735, 735*t*

O

Obesity, 704–706, 705*t*
gas exchange and, 586, 586*f*
Obstetric effects, of inhaled anesthetics, 137–138, 137*f*
Obstructive jaundice, 873
Obstructive nephropathy, 424

Obstructive sleep apnea (OSA), 238
Occipital cortex, 60, 60*f*
Ocular effects, of epinephrine, 453
Ocular inflammation, 788
Oil:gas partition coefficients, of inhaled anesthetics, 105, 113
Olfactory cortex, 60
Olfactory receptors, 75
Omega-3 fatty acids, 550
One-compartment model, 27–30, 28*f*
One-lung ventilation (OLV), 590–591
Ophthalmic venous obstruction, 73
Opioid agonist-antagonists, 207*t*, 230–231, 230*f*
Opioid agonists, 207*t*, 214–228, 215*t*, 216*f*, 217*f*, 218*f*, 220*f*, 221*f*, 222*f*, 223*f*, 228*f*
Opioid antagonists, 207*t*, 231–233, 231*f*
“Opioid Crisis,” 238
Opioids, 206
abuse-resistant, 233
allergies to, 233
anesthetic requirements and, 234
chemical structure of, 206, 207*f*
classification of, 207*t*
clearance of, propranolol and, 478
endogenous pain modulating mechanisms of, 209, 209*f*
gastric emptying and, 693
immune modulation with, 233–234, 234*f*
in lungs, 608
magnesium and, 252
MAO inhibitors and, 863
maternal use of, 897*t*–898*t*
neuraxial, 235–238
pharmacokinetics of, 30–31
side effects of, 236–238, 237*f*
with oral bioavailability, 228–230
for PCA, 234, 235*f*, 235*t*
as peripherally acting analgesics, 268
pharmacodynamic tolerance of, 214, 214*t*
pulmonary circulation and, 603
receptors for, 177, 207–209, 208*t*
safety issues with, 238
semisynthetic, 206
side effects of, 209–213, 210*f*, 211*f*
synthetic, 206, 207*f*
tamper-resistant, 233
tricyclic antidepressants and, 866
withdrawal from, 214, 214*t*, 229
Opioid tolerance, reversal of, 180
Optical isomers, 42–44
Optic neuritis, with antimicrobials, 811*t*
Oral administration, 24–25
Oral contraceptives, 796–797
Oral transmucosal administration, 25

Organelles, 5, 5*f*
Oropharynx, anatomy of, 553, 554*f*
Orthostatic hypotension
in elderly patients, 924
levodopa and, 350–351
OSA. *See* Obstructive sleep apnea
Osmolality, 3
Osmolarity, 3
Osmoreceptor-arginine vasopressin hormone, 421
Osmosis, 2–3, 3*f*
Osmotic diuretics, 536*f*, 537*t*, 540–541
Osteoporosis, corticosteroids and, 790
Ototoxicity, with antimicrobials, 811*t*, 818
Ovarian hormones, 763, 795–797, 795*f*, 796*f*, 797*f*
Overdose
with benzodiazepines, 170, 878
with MAO inhibitors, 863
with NSAIDs, 263–264, 263*t*
with opioids, 213
with phenylephrine, 459–460
with tricyclic antidepressants, 866–867
Overpressure, 104
Oxidation, 18
Oxygen transport, 580–581, 580*f*, 581*f*
uteroplacental, 911, 911*f*
Oxyhemoglobin, 98, 580–581, 580*f*, 581*f*
dissociation curve of, 581, 581*f*
Oxytocin, 53*t*, 754*t*, 758, 795

P

Pain, 195. *See also* Opioids
acute to chronic transition, 201
aging and, 931
central nervous system and, 196, 198*f*
ascending pathway for, 200
central sensitization, 199–200
descending pathway for, 200–201, 200*f*
dorsal horn, 197–199, 198*f*
gate theory for, 199, 199*f*
supraspinal modulation, 200
complex regional syndromes, 202–203
embryologic origin of, 204, 204*f*
fetal, 915–916, 915*f*, 916*t*
localization of, 204, 204*f*
in neonates and infants, 204
neurobiology of, 195
neuropathic, 202
opioid-sensitive endogenous modulation system for, 209, 209*f*
peripheral nerve physiology of, 195–196, 197*f*
during pregnancy, 913

psychobiology of, 201–202
receptors for, 195–196, 197*f*
societal impact of, 195
visceral, 202, 203*f*
Pancreas, 695, 764–767
glucagon, 766–767, 766*t*, 767*f*
insulin, 764–765, 764*f*, 765*f*, 765*t*
pancreatic polypeptide, 767
somatostatin, 767
Pancreatic polypeptide, 767
Pantothenic acid, 740*t*, 741*f*, 742
Papilledema, 71–72
Paradoxical sleep, 63
Paradoxical vocal cord motion, benzodiazepines and, 168
Parasympathetic nervous system, 77–78
acetylcholine in, 82–83
anatomy of, 80–81, 83*f*
dysfunction of, 84–85, 85*t*
residual tone of, 84
responses to stimulation of, 79*t*
Parathyroid glands, 759
Parathyroid hormone (PTH), 759
Parenteral nutrition, 737–739
long-term, 737
short-term, 737
side effects of, 737–738, 738*t*
Parietal cells, 690–691, 691*f*
Parietal cortex, 60, 60*f*
Parkinson disease
amantadine for, 353
anticholinergic drugs for, 353
COMT inhibitors, 352
drugs for, 349–354
levodopa for, 349–352
MAO-B inhibitors for, 353
nonpharmacologic treatment for, 354
peripheral decarboxylase inhibitors for, 352
synthetic dopamine agonists for, 352–353
Partial agonists, 12, 13*f*, 14, 14*f*
Partial seizures, 338*t*
Partial thromboplastin time, 633
Partition coefficients. *See* Blood:gas partition coefficients; Oil:gas partition coefficients, of inhaled anesthetics; Tissue:blood partition coefficients, of inhaled anesthetics
Pasteurization, 823
Patch clamping, 52
Patient-controlled analgesia (PCA)
nausea and vomiting with, 250
opioids for, 234, 235*f*, 235*t*
PCCs. *See* Prothrombin complex concentrates
PEEP. *See* Positive end-expiratory pressure
Pellagra, 742

Peptic ulcer disease, 790
Perfusion distribution, 574–575, 576f
ventilation matching with, 575, 576f, 577f, 578
Pericardium, anatomy of, 388
Perioperative bleeding, management of, 637, 638*t*, 642*t*
use of prothrombin complex concentrates for, 644
Perioperative hearing impairment, 75
Perioperative hemostasis, 644, 656, 657f
Perioperative hypothermia
adverse effects of, 91, 91*t*
beneficial effects of, 90
prevention of, 91–92
Perioperative temperature changes, 89–92
during anesthesia, 89–90, 90*f*
measurement of, 91
Perioperative β -adrenergic receptor blockade, 485, 485*t*
Peripheral decarboxylase inhibitors, for Parkinson disease, 352
Peripherally acting analgesics, 257
capsaicin, 267
NSAIDs, 257–264, 258*f*, 260*t*–261*t*
opioids, 268
steroids, 264, 265*t*
systemic local anesthetics, 264–267
Peripheral nerve block anesthesia, with local anesthetics, 288*t*, 290–291
Peripheral nerve fibers. *See* Afferent nerve fibers, classification of
Peripheral nerves, 50–51
pain and, 195–196, 197*f*
Peripheral nervous system, 76, 77*f*
pathways of
for motor responses, 76
for sensory impulses, 76, 78*f*
Peripheral neuropathy
with antimicrobials, 811*t*
with inhaled anesthetics, 139
Peripheral venous pressure, 365
Peristalsis, 689
Peritubular capillaries, 417, 419
PET. *See* Positron emission tomography
Phagocytosis, 7, 7*f*
Pharmacodynamics, 38–42
of aldosterone receptor antagonists, 541
of barbiturates, 173–175, 174*f*, 175*f*
of carbonic anhydrase inhibitors, 535
concentration *vs.* response relationships, 38–40, 40*f*
of dopamine receptor agonists, 542
drug interactions, 41–42, 42*f*, 43*f*, 44*f*
effective and lethal dose, 41, 41*f*
of inhaled anesthetics, 110–116
mechanisms of action, 113–116, 114*f*
minimal alveolar concentration, 110–113, 110*f*, 111*t*, 112*f*, 113*f*
of loop diuretics, 536–537

of opioids, 214, 214*t*
of osmotic diuretics, 540
of potassium-sparing diuretics, 541
potency and efficacy, 40–41, 41*f*
of selective relaxant binding agents, 323–324
of succinylcholine, 315
of thiazide diuretics, 539
of vasopressin receptor antagonists, 543
Pharmacogenetics, 46
Pharmacogenomics, of succinylcholine, 315
Pharmacokinetics, 15
absorption, 22, 30
of acetylcholinesterase inhibitors, 322
of α -adrenergic receptor agonists, 504
of α -adrenergic receptor antagonists, 502
of β -adrenergic receptor antagonists, 474–475, 477–478, 479, 480–481
of aldosterone receptor antagonists, 541
of antiepileptic drugs, 337–338, 342*t*, 343–346, 348
of antipsychotic drugs, 870
of barbiturates, 173–176, 173*f*–175*f*
of benzodiazepines, 164–165, 165*t*, 168–169, 168*f*, 171
bolus, 27–29, 28*f*
of calcium channel blockers, 488*t*, 489, 489*t*, 491, 492, 493–494
of cannabinoids, 881
of carbonic anhydrase inhibitors, 535
of cardiac glycosides, 462, 462*f*
of cocaine, 297
of combined α - and β -adrenergic receptor antagonists, 486
context-sensitive half-time, 36–38, 40*f*
of corticosteroids, 784–785
distribution, 15–16, 16*f*
of dopamine receptor agonists, 542
dose calculations
bolus dosing, 33–35, 34*f*, 35*t*
maintenance infusion rate, 35–36, 37*f*, 38*f*, 39*f*
of fibrates, 549–550
of GABA agonists, 151–152, 151*f*, 151*t*, 158–159
of gastrointestinal prokinetics, 729
of H₁-receptor antagonists, 719*t*, 720
of H₂-receptor antagonists, 722–724
of heparin, 660
hepatic clearance, 18–22, 19*f*, 20*f*, 21*f*
infusion, 29–30
of inhaled anesthetics, 97*f*, 100–110
alveolar partial pressure, 101–103, 101*f*–103*f*, 101*t*
alveolar-to-venous partial pressure differences, 107–108, 107*t*
cardiac output, 106–107
recovery from, 99*f*, 108–110, 108*f*, 109*f*
solubility, 103–106, 104*t*, 105*f*, 106*f*
ionization, 22–24, 23*t*
linear, 29

of local anesthetics, 277–281
absorption and distribution, 277, 277*f*
adjuvant mixed with, 280
alkalinization, 280
combinations of, 281
lung extraction, 277
placental transfer of, 278, 278*f*
renal elimination and clearance, 278
vasoconstrictors with, 281, 281*f*
of loop diuretics, 536–537
metabolism, 17
pathways of, 17–18
rate of, 18–22, 19*f*
models of, 25–32
compartmental, 26–32, 28*f*
physiologic, 26, 27*f*
zero- and first-order processes, 25–26, 26*f*
of neuraxial opioids, 235–236
of niacin, 549
of nitrodilators, 511
of non- γ -aminobutyric acid sedative-hypnotics, 177–178, 184
of opioid agonist-antagonists, 230
of opioid agonists, 215–216, 215*t*, 216*f*, 217*f*, 218, 218*f*, 219–220, 220*f*, 221*f*, 223–226
of oral glucose regulators, 773, 774, 776
of osmotic diuretics, 540
of potassium-sparing diuretics, 541
of proprotein convertase subtilisin/kexin type 9, 548
protein binding, 16–17
renal clearance, 22, 22*f*
route of administration, 24–25
of selective relaxant binding agents, 323
of statins, 547
of succinylcholine, 315
of thiazide diuretics, 539
time course of drug effect, 32–33, 32*f*, 33*f*
of tricyclic antidepressants, 865–866
of vasopressin receptor antagonists, 543
of warfarin, 665–666
Pharynx
anatomy of, 553, 554*f*
innervation of, 555–556
Phase I enzymes, 17–18
Phase II enzymes, 18
Phenylalkylamines, 490–491, 491*f*
Pheochromocytoma, 794
diagnosis of, 84
excessive circulating norepinephrine in, 58, 82
magnesium and, 441
symptoms of, 85
Phosphate, in intravenous fluids, 445–446
Phosphate buffering systems, 619

Phosphodiesterase inhibitors, 464–466, 465*f*, 507
pulmonary circulation and, 606
Phospholipids, 687, 700, 700*f*, 701*f*, 702*t*
Phosphorus depletion, 718–719
Photosensitivity, with antimicrobials, 812*t*
pH-stat management, 625, 625*t*
PHTN. *See* Pulmonary hypertension
Physical dependence, opioids, 214, 214*t*
Physiologic models of pharmacokinetics, 26, 27*f*
PI, of inhaled anesthetics. *See* Inhaled partial pressure, of inhaled anesthetics
Piezoelectric effect, 442
Pinocytosis, 7, 7*f*
Pipecoloxylide, 273, 273*f*
Pituitary gland, 71*f*
anterior, 754*t*, 755–757, 755*f*, 755*t*, 756*t*
drugs for, 792
hormones of, 754, 754*t*
melatonin, 792–793, 793*f*
posterior, 754*t*, 757–758, 757*t*
drugs for, 793–795
Placental transfer
of β -adrenergic receptor antagonists, 483
of local anesthetics, 278, 278*f*
opioids and, 213
Plasma, 1, 2*f*, 3*f*
cryoprecipitate, 637, 638*t*, 641
ions and urea in, 422–423, 422*f*
solvent/detergent-treated, 640–641
transfusion of, 636, 638*t*, 639–641
Plasma cholinesterase. *See* Butyrylcholinesterase
Plasma colloid osmotic pressure, 382, 385
Plasma proteins, 703–704
Platelet function
antimicrobials and, 811*t*
benzodiazepines and, 164
calcium channel blockers and, 495
in clotting, 631
GABA agonists and, 156
nitrodilators and, 510
non- γ -aminobutyric acid sedative-hypnotics and, 182
NSAIDs and, 259
Platelet glycoprotein IIb/IIIa antagonists, 669–670
Platelet inhibitors, 668–670, 669*t*, 670*f*, 671*f*
Platelet transfusions, 636, 638*t*, 642*t*
alloimmunization, 641, 642
graft versus host disease, 643
indications for, 643–644
leukoreduction, 642–643
for massive transfusion coagulopathy, 680
Platinating drugs, 839
Platinum compounds, 831*t*

Polymodal nociceptors, 196
Positive end-expiratory pressure (PEEP), 568
auto- and intrinsic-, 590
obesity and, 586, 586*f*
Positron emission tomography (PET), 67
Posterior pituitary gland
drugs for, 793–795
hormones of, 754*t*, 757–758, 757*t*
Postintubation laryngeal edema, 788
Postoperative analgesia, corticosteroids for, 787
Postoperative bleeding, 637, 638*t*
Postoperative blindness, 73
Postoperative cognitive dysfunction, 62
Postoperative hypercoagulability, 633–634
Postoperative nausea and vomiting (PONV), 707–714
incidence of, 707
pathophysiology of, 707–708, 708*f*
pharmacologic interventions for, 708–714
anticholinergics, 709*t*, 711–712
benzamides, 712–713
benzodiazepines, 709*t*, 714
butyrophenones, 713
corticosteroids, 709*t*, 712
dopamine antagonists, 712–713
histamine receptor antagonists, 709*t*, 712
5-HT3 receptor antagonists, 709–710, 709*t*
prevention of, 711
prophylaxis for, 708
Postoperative sedation
benzodiazepines for, 167–168
non- γ -aminobutyric acid sedative-hypnotics for, 185
Postpartum hemorrhage, 680–681
Postrenal obstructive nephropathy, 424
Postsynaptic density, 53*f*, 58, 59*f*
Postsynaptic membrane, 58, 59*f*, 306, 307*f*, 308
Posttetanic facilitation, 59
Potassium
 β -adrenergic receptor antagonists and, 482–483, 483*f*
calcium channel blockers and, 494
epinephrine and, 452, 453*f*
in intravenous fluids, 444–445
in ion channels, 55
plasma concentration of, 422, 422*f*
role of, 444
Potassium ion channel blockers, 519–520
Potassium-sparing diuretics, 512, 536*f*, 537*t*, 541
Potency, 40–41, 41*f*
PPIs. *See* Proton pump inhibitors
Preeclampsia, 440
Preexcitation syndrome, 407, 408*t*
Pregnancy, 763. *See also* Maternal physiology; Uteroplacental physiology

antimicrobials during, 812, 813*t*
local anesthetics and, 277–278
MAC of inhaled anesthetics during, 112
pain during, 913
Preload, 398–399, 399*f*
Premature atrial contractions, 409, 409*f*
Premature ventricular contractions, 410, 411*f*
Premotor cortex, 60, 60*f*
Preoperative hypokalemia, 452
Preoperative medication
ACE inhibitors for, 506
barbiturates for, 173
benzodiazepines for, 166, 167*f*
Prerenal azotemia, 423
Pressure-volume loops, 373, 373*f*, 398–399, 399*f*
Presynaptic membrane, 58, 59*f*
Presynaptic terminal, 49
of NMJ, 306, 307–310, 307*f*
Primary hyperalgesia, 196
P-R interval, 394, 394*f*
Procoagulants
antifibrinolytic agents, 651–652
desmopressin, 653–654
fibrinogen, 654
for massive transfusion coagulopathy, 680
protamine, 652–653, 653*f*
recombinant coagulation products, 654–656, 655*t*
topical hemostatic agents, 656
Proconvulsant activity, with GABA agonists, 157
Progesterone, 763, 796, 797*f*
Prolactin, 53*t*, 754*t*, 756, 756*t*
Propofol infusion syndrome, 157
Proprotein convertase subtilisin/kexin type 9 (PCSK9), 546*f*, 547*t*, 548
Prostacyclin, 382–383
Prostaglandins, pulmonary circulation and, 605–606, 606*f*
Protein binding, 16–17
 β -adrenergic receptor antagonists and, 476*t*, 477, 477*f*
antiepileptic drugs and, 337–338
benzodiazepines and, 168
Protein buffering systems, 619
Protein C, 632–633
Protein catabolism, 761
Protein-mediated transport, 9
Protein metabolism, 687, 702–704, 702*t*, 703*f*, 703*t*
Proteins
in body fluids, 2, 3*f*
types of, 701*t*
Protein S, 632–633
Prothrombin complex concentrates (PCCs), 644, 656
Prothrombin time, 632–633
prolonged, 811*t*

Proton pump inhibitors (PPIs), 727–728, 727*t*, 728*f*
Pruritus, with neuraxial opioids, 236
Pseudocholinesterase. *See* Butyrylcholinesterase
Pseudounipolar neuron, 76
Psychiatric disturbances, levodopa and, 351
Psychopharmacologic drugs, 854–882
drugs with serotonergic activity, 854–864, 855*t*, 856*t*
Pteridine analogues, 541
PTH. *See* Parathyroid hormone
Pulmonary acinus, 557
Pulmonary arrest, 935, 938–939, 941–942
Pulmonary artery occlusion pressure, 381
Pulmonary blood flow. *See* Cardiac output
Pulmonary capillaries, 562*f*
Pulmonary circulation, 380–386, 562–563, 562*f*, 574
anatomy of, 380–381, 380*f*
anesthetics and, 602–603
blood flow and distribution, 382–384, 382*f*
blood volume, 382, 382*f*
hypoxic pulmonary vasoconstriction and, 606–607
interstitial fluid space, 381–382
magnesium and, 603–604
neuromuscular blockers and, 603
nitric oxide and, 604–605, 605*f*
opioids and, 603
pathology of, 385–386, 386*t*
pharmacology of, 602–607
phosphodiesterase inhibitors and, 606
prostaglandins and, 605–606, 606*f*
pulmonary vasodilators and, 604
regional analgesia and, 604
vascular pressure, 381, 381*f*
vasopressors and inotropes and, 604
volatile anesthetics and, 603
Pulmonary edema, 385, 647
Pulmonary embolism, 385, 610, 927
Pulmonary function testing, 565*f*
Pulmonary hemodynamics, 574
Pulmonary hypersensitivity reaction, 646
Pulmonary hypertension (PHTN), 385–386, 386*t*, 602
Pulmonary lymph vessels, 381
Pulmonary shunt, 577*f*, 578–579, 578*f*
Pulmonary system
acetylcholinesterase inhibitors and, 322
chemotherapeutic drugs and, 844–845, 844*f*, 845*t*
maternal, 904*t*, 906–909, 907*f*, 907*t*, 908*f*
nitrodilators and, 510
NSAIDs and, 261–262
Pulmonary vascular resistance, inhaled anesthetics and, 122
Pulmonary vasodilators, 604
Pulse contour analysis, 375

Pulse deficit, 364
Pulse pressure, in arteries, 362–363, 362*f*
Pulsus alternans, 364
Pulsus paradoxus, 363–364
Pupil, 72, 72*f*
Purified protein concentrates, 644–645
fibrinogen concentrates, 644
prothrombin complex concentrates, 644
von Willebrand factor, 644–645
Purine analogues, 832*t*, 841–842
Purkinje fibers, 390, 391*f*
P wave, 394
Pyramidal tracts, 64–65, 65*f*
Pyridoxine (vitamin B₆), 740*t*, 741*f*, 742
levodopa and, 352
Pyrimidine analogues, 831*t*, 840–841
Pyrogens, fever and, 88

Q

QRS complex, 395
QTc interval
with antimicrobials, 812*t*, 819
antipsychotic drugs and, 872
with inhaled anesthetics, 123
QT interval, 395
Quaternary ammonium compounds, 822–823
Q wave, 394–395

R

Racemic mixture, 43–45
Rapid eye movement (REM) sleep, 63
RBCs. *See* Red blood cells
RE. *See* Response entropy
Rebound hypertension, 504
Receptors, 12, 13*f*, 52–53
action of, 15
 α_2 -adrenergic, 246
 β_2 -adrenergic, 54*f*
for benzodiazepines, 13*f*, 14, 57, 69
classification of, 53
concentration of, 58
conformations of, 14, 14*f*
dihydropyridine, 310, 311*f*
diseases of, 58
drug interactions at, 41–42, 42*f*, 43*f*, 44*f*
enzyme-linked transmembrane, 53
g-aminobutyric acid, 14–15, 57, 69, 162, 162*f*, 251
G protein-coupled, 53–55, 54*f*
ionotropic

glutamate, 57
inhaled anesthetics and, 114–115
ligand-gated ion channels, 55
metabotropic
glutamate, 57
G protein-coupled receptors and, 55
inhaled anesthetics and, 114–115
monoaminergic, 177
muscarinic, 54*f*, 56, 57, 177
neuronal nicotinic acetylcholine, 177
neurotransmitter interactions with, 53*f*, 80*t*
acetylcholine, 83
norepinephrine, 82
nicotinic acetylcholine, 56–57, 58, 81, 86
at NMJ, 308–310, 309*f*
N-methyl-D-aspartate, 177, 177*f*, 249–250
olfactory, 75
opioid, 177, 207–209, 208*t*
pain, 195–196, 197*f*
ryanodine, 310, 311*f*
serotonin, 855
types of, 15
Recombinant coagulation products, 654–656, 655*t*
Recovery, from inhaled anesthetics, 99*f*, 108–110, 108*f*
context-sensitive half-time, 109–110, 109*f*
diffusion hypoxia, 110
Rectal administration, 25
Red blood cells (RBCs)
in massive transfusion coagulopathy, 676
storage and tissue oxygenation parameters for, 639
storage lesions, 639
for transfusion, 637–639, 638*t*
Reduction, 18
Reentry circuit, 407
Reflex vasoconstriction, 87, 90
Refractory period, 51*f*, 52
Regional analgesia, pulmonary circulation and, 604
Regional anesthesia, with local anesthetics, 287–297, 288*t*–289*t*
Relative refractory period, 52
Release apparatus, 58
REM sleep. *See* Rapid eye movement sleep
Renal blood flow, 419–420, 419*f*, 420*f*
anesthesia and, 427–429, 427*f*, 428*t*
Renal-body fluid system, 371
Renal clearance, 22, 22*f*
of benzodiazepines, 165
of local anesthetics, 278
Renal-dose dopamine, 455–456
Renal function
in elderly patients, 929
GABA agonists and, 156

hydrogen ion concentration and, 620–621, 620*f*
inhaled anesthetics and, 134–136, 135*f*, 136*f*
lithium and, 879
maternal, 904*t*, 909, 910*f*
nitrodilators and, 509
NSAIDs and, 259–261
Renal natriuretic peptide (urodilatin), 421
Renal physiology, 415. *See also* Kidney
acute kidney injury, 423–426, 424*f*, 425*f*
anesthesia and, 426–429
body fluid regulation, 420–423, 421*f*, 422*f*
kidney function measurement, 423
kidney structure and function, 415–419, 416*f*, 417*t*, 418*f*
of neonates, 891–892
renal blood flow, 419–420, 419*f*, 420*f*
anesthesia and, 427–429, 427*f*, 428*t*
tubular transport maximum, 418–419, 418*f*
Renal tubule
function of, 417–418, 417*t*, 418*f*
structure of, 416*f*, 417
Renin-angiotensin system, 371
Reperfusion injury, 158
Repolarization, 51, 51*f*
Reproductive glands
menopause, 763
menstruation, 763
ovaries, 763
pregnancy, 763
testes, 762–763
Rescue technique, 840
Resistance of respiratory system, 570–573, 571*f*
Respiratory acidosis, 621–622, 624–625
Respiratory airways, 557–562, 560*f*–562*f*
Respiratory alkalosis, 621*t*, 622, 625
Respiratory arrest, 935, 938–939, 941–942
Respiratory bronchioles, 557
Respiratory control
central nervous system in, 583–584, 583*f*
neural connections in, 584
peripheral chemoreceptors in, 583*f*, 584
Respiratory distress syndrome, 788–789
Respiratory effects
of dopamine, 456
of neuromuscular-blocking drugs, 322
Respiratory fatigue, 574
Respiratory mechanical function, 564, 564*f*, 565*f*
Respiratory muscles, 563
Respiratory physiology, of neonates, 890–891, 891*t*
Respiratory system
compliance of, 568–570, 570*f*, 571*f*
of elderly patients, 924–927, 925*t*, 926*f*

resistance of, 570–573, 571*f*
Response entropy (RE), 69
Response relationships, concentration *vs.*, 38–40, 40*f*
Resting membrane potential, 51, 55
Restless leg syndrome, 180
Restrictive lung diseases, 590
Resuscitation, 935–942
cardiopulmonary, 935, 939–941, 939*f*
hemorrhage, 941
multimodal, 681
oxygenation/ventilation, 941–942
pathophysiology of, 936–939, 937*f*
cardiac arrest, 935, 936–938, 939
hemorrhagic shock, 938
respiratory arrest, 935, 938–939, 941–942
Reticular activating system, 60*f*, 63
Retina, 72–73, 72*f*
Retinal occlusion, 73
Retinoic acid, 740*t*, 745–746, 745*f*
Retinol, 740*t*, 745–746, 745*f*
Reuptake, of norepinephrine, 82
Riboflavin (vitamin B₂), 740*t*, 741–742, 741*f*
RIFLE criteria, 424–426, 425*f*
Right atrial pressure, 364–366
inhaled anesthetics and, 122, 122*f*
Rigidity, opioids and, 212
RNA, 9–10
Route of administration, 24–25
R wave progression, 395
Ryanodine receptor (RyR1), 310, 311*f*

S

Salivary glands, 689
Saltatory conduction, 50, 50*f*
SA node. *See* Sinoatrial node
Saturation equation, 19, 19*f*
Saw palmetto, 749*t*
SCD. *See* Sudden cardiac death
SCh. *See* Succinylcholine
Scurvy, 744–745
SE. *See* Spectral entropy
Secondary hyperalgesia, 196
Second-gas effect, of inhaled anesthetics, 102, 102*f*
Sedation
with antipsychotic drugs, 873
intravenous. *See* Intravenous sedation
opioids and, 212
neuraxial, 237
postoperative. *See* Postoperative sedation
Sedative-hypnotics, 150

barbiturates, 172–176, 173*f*–175*f*
benzodiazepines, 161–172, 162*f*, 164*f*–170*f*, 165*t*, 170*t*
 γ -aminobutyric acid agonists, 150–161, 151*f*, 151*t*, 153*f*–156*f*, 160*f*, 161*f*, 878
maternal use of, 899*t*
non- γ -aminobutyric acid, 176–185, 177*f*, 178*f*, 180*f*, 181*t*, 183*f*–185*f*
Sedatives, 150
Seizure activity
with antimicrobials, 811*t*
with antipsychotic drugs, 873
with benzodiazepines, 170, 170*f*
in epilepsy, 69, 337, 338, 338*t*
with GABA agonists, 157
with inhaled anesthetics, 117
with opioid agonists, 222
Selective cardiac toxicity, local anesthetics and, 284–285, 284*f*
Selective phosphodiesterase inhibitors, 464–466, 465*f*
Selective relaxant binding agents, 323–326
adverse effects of, 325–326
chemistry of, 323, 323*f*
drug interactions with, 325
pharmacodynamics of, 323–324, 324*f*, 325*f*
pharmacokinetics of, 323
Selective serotonin reuptake inhibitors (SSRIs), 856*t*, 858–859
Selective β_2 -adrenergic receptor agonists, 452, 453*f*, 460–461, 460*f*, 460*t*
Selenium, in intravenous fluids, 447–448
Semisynthetic colloid solutions, 434–438, 435*t*, 436*t*, 437*t*, 438*t*
Semisynthetic opioids, 206
Sensorimotor cortex, 60, 60*f*
Sensory cortex, 60, 60*f*
Sensory impulses, pathways for peripheral, 76, 78*f*
Sepsis
loss of glycocalyx in, 378, 378*f*
with TPN, 738
Septic shock, 373–374, 789, 794
Serotonergic drugs, 854–864, 855*t*, 856*t*
mechanism of action, 855
monoamine oxidase inhibitors, 856*t*, 861–864
serotonin agonists, 731, 856*t*, 860
serotonin and norepinephrine multimodal drugs, 856*t*, 860–861
serotonin multimodal drugs, 856*t*, 860
serotonin reuptake inhibitors, 855–860, 856*t*
Serotonin (5-HT)
in excitatory ligand-gated ion channels, 57
G protein-coupled receptors and, 55
in lungs, 610
as neurotransmitter, 53*t*
Serotonin and norepinephrine multimodal drugs, 856*t*, 860–861
Serotonin multimodal drugs, 856*t*, 860
Serotonin-norepinephrine reuptake inhibitors, 856*t*, 859
Serotonin (5-HT) receptor agonists, 856*t*, 860
for gastrointestinal motility, 731

Serotonin (5-HT) receptor antagonists
for gastrointestinal motility, 731
for PONV, 709–710, 709*t*
Serotonin receptors, 855
Serotonin reuptake inhibitors (SRIs), 855–860
Serotonin syndrome, 219, 857–858, 858*t*
SGLT2. *See* Sodium-glucose cotransporter 2 inhibitors
Shivering, 88
Shock, opioid antagonists for, 232
Shock syndromes, 373–374
Short-term memory, 61
Shunt
inhaled anesthetics and, 107
of venous blood, 577*f*, 578–579, 578*f*
SIG. *See* Strong ion gap
Signal transduction modulators, 829*t*, 834*t*–835*t*, 847–848
Single-photon emission computed tomography (SPECT), 67
Single twitch, 327, 331*f*
Sinoatrial (SA) node, 390–391, 391*f*
Sinus bradycardia, 408, 409*f*
Sinus dysrhythmias, 409, 409*f*
Sinus tachycardia, 408, 408*f*
Skeletal muscle effects
of antimicrobials, 818
of antipsychotic drugs, 873
of benzodiazepines, 169
of corticosteroids, 791
of inhaled anesthetics, 136–137, 137*f*
of statins, 548
Skeletal muscles
contraction of, 310–311, 312*f*
in elderly patients, 929–930, 930*t*
motor units of, 305, 306*f*
neuromuscular transmission and excitation-contraction coupling, 310–313, 311*f*, 312*f*
types of, 305
Sleep
desynchronized, 63
slow-wave, 63
Sleep apnea, obstructive, 238
Sleep-disordered breathing, 586–587, 927
Slow-wave sleep, 63
Small intestine, 693–694, 694*t*
Smell, 75
Smooth muscle, 311–312
epinephrine and, 452
functions of, 305
uterine, 313
Sodium
in ion channels, 55
plasma concentration of, 422
Sodium channel blockers, 518–519, 876. *See also* Voltage-gated sodium channels

Sodium-glucose cotransporter 2 inhibitors (SGLT2), 773*t*, 776
Sodium ion cotransport, 9
Sodium-potassium adenosine triphosphatase, 7, 7*f*
Sodium-potassium pump (ATPase), 51, 452
Solubility
alveolar ventilation and, 103
of inhaled anesthetics, 103–106, 104*t*
blood:gas partition coefficients, 104–105, 104*t*, 105*f*
cardiopulmonary bypass, 106
 N_2O transfer to closed gas spaces, 105–106, 106*f*
oil:gas partition coefficients, 105, 113
tissue:blood partition coefficients, 105
Solvent/detergent-treated plasma, 640–641
Soma, 49
Somatosensory evoked potentials, 69–70
with barbiturates, 175
with non- γ -aminobutyric acid sedative-hypnotics, 181
with opioid agonists, 222–223
Somatostatin, 754*t*, 755*f*, 755*t*, 765*t*, 767
Somatotropin. *See* Growth hormone
Somesthetic cortex, 60
SP. *See* Substance P
SPECT. *See* Single-photon emission computed tomography
Spectral entropy (SE), 69
Spinal anesthesia, with local anesthetics, 293, 294*f*
Spinal cord, 59–60, 64–67
autonomic reflexes, 66
covering membranes of, 66
gray matter, 64, 64*f*
nerves of, 65–66, 66*f*
pyramidal and extrapyramidal tracts, 64–65, 65*f*
shock of, 66
thalamocortical system, 65
white matter, 64
Spinal hematoma, 662
Spinocervical tracts, 76
Spinothalamic tracts, 76
Spirometry, 564–567, 566*f*
Spontaneous breathing
with inhaled anesthetics, 123, 128
mechanical ventilation *vs.*, 102–103, 103*f*
SRIs. *See* Serotonin reuptake inhibitors
SSRIs. *See* Selective serotonin reuptake inhibitors
Statins, 546–548, 546*f*, 547*t*
 α -stat strategy, 625–626, 625*t*
Status epilepticus, 69, 349
Stereochemistry, 42–45
Stereoselectivity, of inhaled anesthetics, 114, 114*f*
Sterilization, 823–824
Steroids, 264, 265*t*
as nondepolarizing neuromuscular block, 319

St. John's wort, 749*t*, 750
Stomach, 690–691, 691*f*
Stress, metabolism and, 704–706
Stretch reflex, 76
Stroke volume, inhaled anesthetics and, 121, 121*f*
Strong ion gap (SIG), 623
Strychnine, 57
ST segment, 395, 395*f*
Sublingual administration, 25
Substance P (SP)
airway and, 595
G protein-coupled receptors and, 55
as neurotransmitter, 53*t*
Substantia gelatinosa, 64
Succinylcholine (SCh), 308
hyperkalemia with, 317, 445
side effects of, 317–318
structure-activity relationships for, 315
Sudden cardiac death (SCD), 936, 937
Suicidality, 250, 857
Superficial dorsal horn, 198
Surgical stimulation, inhaled anesthetics and, 127–128, 128*f*
SVs, of NMJ. *See* Synaptic vesicles, of NMJ
Sympathetic nervous system, 77–78
acute denervation of, 86
 β -adrenergic receptor antagonists and, 486
anatomy of, 78–79, 81*f*, 82*f*
antimicrobials and, 812*t*
chronic stimulation of, 85–86
denervation hypersensitivity, 86
dysfunction of, 84–85, 85*t*
norepinephrine in, 81–82, 84*f*
residual tone of, 84
responses to stimulation of, 79*t*
Sympatholytics
 α -adrenergic receptor agonists, 473–474, 503–505, 503*f*
 α -adrenergic receptor antagonists, 471–474, 472*f*
 α_1 -, 501*t*, 502–503
 β -adrenergic receptor antagonists, 474–486, 501–502, 501*t*
benzothiazepines, 493–494
calcium channel blockers, 487–496, 488*f*, 501*t*, 506–507
combined α - and β -adrenergic receptor antagonists, 486–487, 486*f*
dihydropyridines, 491–493, 506–507
phenylalkylamines, 490–491, 491*f*
Sympathomimetics
MAO inhibitors and, 863
tricyclic antidepressants and, 866
Synapses, 49, 58–59
modulation of, 58
structure of, 53*f*, 58, 59*f*
Synaptic cleft, 49, 53*f*

action potential across, 58, 59*f*
of NMJ, 306, 308, 308*f*
Synaptic fatigue, 59
Synaptic vesicles (SVs), of NMJ, 53*f*, 307–308, 307*f*
Syncope, 368
Synthetic catecholamines, 456–458
Synthetic dopamine agonists, for Parkinson disease, 352–353
Synthetic noncatecholamines, 458–460, 458*f*–460*f*, 460*t*
Synthetic opioids, 206, 207*f*
Systemic blood pressure
measurement of, 361
progressive declines in, 361–362, 361*f*
regulation of, 369–371
long-term mechanisms for, 371
moderately rapid-acting mechanisms for, 371
rapid-acting mechanisms for, 369–371, 369*f*, 370*f*
respiratory variations in, 370–371
vasomotor waves of, 371
Systemic circulation, 359–364
blood viscosity, 366, 366*f*
components of, 359–360
endothelial function in, 359, 360*t*
lymphatics, 379–380, 379*f*
microcirculation. *See* Microcirculation
physical characteristics of, 360–364, 360*f*, 361*t*
auscultation measurement of blood pressure, 361
after cardiopulmonary bypass, 363–364, 363*f*
declines in blood pressure, 361–362, 361*f*
hydrostatic pressure, 365, 366*f*
measurement of blood pressure, 361
pulse pressure in arteries, 362–363, 362*f*
venous valves and pump mechanism, 365–366
tissue blood flow, 366–367, 367*f*, 367*t*
Systemic hypertension, 500–501, 501*t*
Systemic local anesthetics, 264–267
Systemic vascular resistance
inhaled anesthetics and, 122, 122*f*, 123*f*
maternal, 906

T

T₃. *See* Triiodothyronine
T₄. *See* Thyroxine
TACO. *See* Transfusion-associated circulatory overload
Taste, 75
Taxanes, 833*t*, 846
TEA. *See* Thoracic epidural analgesia
Temporal cortex, 60, 60*f*
Temporal field of vision, 73
Tendinitis, with antimicrobials, 812*t*
Teratogenicity, with antimicrobials, 812*t*

Testes, 762–763
Tetanic stimulus, 329, 331*f*
Tetanus toxin, 57
Thalamocortical system, 65
Thalamus, 60, 60*f*
Theophylline, hypokalemia with, 444
Thermodilution method, 374–375
Thermoregulation, 86–92, 928*t*
in elderly patients, 928
heat loss, 87
hyperthermia, 88, 88*t*
methods for, 87–89
of neonates, 891
nonshivering thermogenesis, 87–88
perioperative temperature changes, 89–92, 89*t*, 90*f*
adverse consequences, 91, 91*t*
during anesthesia, 89–90
beneficial effects of, 90
measurement of, 91
prevention of, 91–92
shivering, 88
Thiamine (vitamin B₁), 739–741, 740*t*, 741*f*
Thiazide diuretics, 536*f*, 537*t*, 539–540, 880*t*
Thiazolidinediones (TZDs), 773*t*, 776
Thienopyridines, 668, 669*t*
Thiocyanate toxicity, 510–511
Thirst reflex, 421–422
Thoracic epidural analgesia (TEA), 604
Thorax, 563
Thrombin
in clot formation, 630–631
inhibitors of, 667
Thrombocytopenia, 634
with antimicrobials, 811*t*
heparin-induced, 662
Thrombolytic drugs, 671
Thyroid gland, 758–759, 758*f*
Thyroid-stimulating hormone (TSH), 754*t*, 757, 779, 780*t*
Thyroid storm, 781–782, 782*t*
Thyrotropin, 754*t*
Thyroxine (T₄), 758–759, 758*f*, 779–782, 780*f*, 780*t*
Tidal volume, with inhaled anesthetics, 127
Tissue blood flow
control of, 367–369, 367*t*
determinants of, 366–367, 367*f*
Tissue:blood partition coefficients, of inhaled anesthetics, 105
Tissue damage, non-γ-aminobutyric acid sedative-hypnotics and, 182
Tissue factor, in clot formation, 630–631
Tissue-specific estrogens, 796
Tm. *See* Tubular transport maximum
TNS. *See* Transient neurologic symptoms, with local anesthetics

α -Tocopherol, 740*t*, 745*f*, 747
TOF stimulation. *See* Train-of-four stimulation
Tolerance, 15
to barbiturates, 46
to tricyclic antidepressants, 865
Tonic-clonic seizures, 69
Tonicity of fluids, 3, 4*f*
Topical anesthesia, with local anesthetics, 288*t*–289*t*, 289
Topical antiseptics, 821–823
Topical hemostatic agents, 656
Topoisomerase inhibitors, 829*t*, 832*t*–833*t*, 842–845, 843*f*, 844*f*, 845*t*
Torsades de pointes, 56, 521, 937
Total anesthetics, 115
opioids for, 234
Total body oxygen requirements, inhaled anesthetics and, 139
Total parenteral nutrition (TPN), 734
monitoring during, 738–739
preparations of solutions for, 739
side effects of, 737–738, 738*t*
Toxicity
of antimicrobials, 811*t*–812*t*
of antipsychotics, 873
of cannabinoids, 881
of cardiac glycosides, 463–464
of lidocaine, 266*f*
of lithium, 880, 880*t*
of methylxanthines, 355
of nitric oxide, 508
of nitrodilators, 510–511
of statins, 548, 548*t*
Trachea, structure of, 556–557, 557*f*, 558*f*, 559*f*
Train-of-four (TOF) stimulation, 316–317, 324, 324*f*, 331*f*
Transcortin, 761
Transdermal administration, 25
Transfusion-associated circulatory overload (TACO), 645–646, 646*t*
Transfusion-related acute inflammatory responses, 648
Transfusion-related acute lung injury (TRALI), 646–648, 646*f*, 647*t*
Transfusion therapy, 637
adverse effects of, 645–648, 646*f*, 646*t*, 647*t*
Transient neurologic symptoms (TNS), with local anesthetics, 286
Traube-Hering waves, 371
Trauma
endothelial dysfunction and, 675
hemostatic abnormalities with, 675
Trauma-induced coagulopathy, 674
Triangle of Koch, 391
Triazenes, 831*t*
Tricyclic antidepressants, 46, 856*t*, 859–860, 864–867
and autonomic nervous system, 80*t*
drug interactions with, 866
mechanism of action of, 864

overdose of, 866–867
pharmacokinetics of, 865–866
side effects of, 864–865, 864*t*
tolerance to, 865
Tricyclic serotonin reuptake inhibitors, 859–860
Triglycerides, 687, 700*f*, 701, 702, 702*t*
Triiodothyronine (T₃), 758–759, 758*f*, 779–782, 780*f*, 780*t*
TSH. *See* Thyroid-stimulating hormone
Tube feeding, 736
Tubular transport maximum (Tm), 418–419, 418*f*
Tubulin-binding drugs, 829*t*, 845–846
Tumescent liposuction, 297
T wave, 395
Two-pore potassium channels, inhaled anesthetics and, 114–115
TZDs. *See* Thiazolidinediones

U

Ulcerative colitis, 788
Unconsciousness, mechanisms of anesthesia-induced, by inhaled anesthetics, 115–116
Upper airway
in elderly patients, 927
gas flow of, 556, 556*f*
larynx, 553–555, 554*f*
oropharynx and nasopharynx, 553, 554*f*
pharyngeal innervation, 555–556
Urea, plasma concentration of, 423
Urinary retention, with neuraxial opioids, 236
Urine, transport to bladder, 419
Urodilatin, 421
Uterine smooth muscle, 313
Uteroplacental physiology, 910–911, 910*f*
oxygen transfer, 911, 911*f*
uterine blood flow, 911
U wave, 395

V

Vaccines, as chemotherapeutic drugs, 835*t*, 849
Valerian, 749*t*, 750
Valvular heart disease
aortic insufficiency, 402, 403*f*
aortic stenosis, 401–402
mitral regurgitation, 403, 404*f*
mitral stenosis, 402–403
Vanillylmandelic acid (VMA), 82
Vaporizers, 96
Vaptans. *See* Vasopressin receptor antagonists
Varicose veins, 366
Vasa recta, 419
Vascular compliance, 367

Vascular distensibility, 367
Vascular tone, endothelial function in, 359
Vasoactive intestinal peptide (VIP), 53*t*, 595
Vasoconstriction, 367
causes of, 84, 86, 91
cutaneous, 89
hypoxic pulmonary, 383–384, 384*f*, 579–580, 579*f*, 606–607
intraoperative, 90
reflex, 87, 90
Vasoconstrictors, with local anesthetics, 281, 281*f*
Vasodilators
nitric oxide and nitrovasodilators, 507–512, 508*f*
pulmonary, 604
sympatholytics for, 501–507, 501*t*, 503*f*
systemic hypertension, 500–501, 501*t*
Vasomotion, 377
Vasomotor center, 368
Vasomotor waves, 371
Vasopressin. *See* Antidiuretic hormone
Vasopressin receptor antagonists, 536*f*, 537*t*, 542–543
Vasopressors, pulmonary circulation and, 604
Veins, 360, 376*t*
Vena cava, 376*t*
Venoconstriction, 367
Venous circulation, 364–375
Venous return, regulation of, 371–375
Venous thromboembolism (VTE)
aging and, 927–928
prophylaxis against, 662
Venous valves, 365–366
Ventilation distribution, 574
perfusion matching with, 575, 576*f*, 577*f*, 578
Ventilation effects
of barbiturates, 175
of benzodiazepines, 166, 169, 169*f*
of GABA agonists, 160
of inhaled anesthetics, 127–130, 127*f*–131*f*, 128*t*
of neuraxial opioids, 236–237, 237*f*
of non- γ -aminobutyric acid sedative-hypnotics, 182
of opioids, 210–211, 226
Ventilatory depressant effects, of inhaled anesthetics, 129
Ventilatory response
to hydrogen ion concentration, 619–620
to hypoxia, local anesthetics and, 287
Ventilatory support, extracorporeal, 591
Ventricular fibrillation, 411, 411*f*
Ventricular function curves, 372–373, 372*f*
Ventricular tachycardia, 411, 411*f*
incessant, 521
Venules, 360, 375–376, 376*f*, 376*t*
Vessel-rich group tissues, 16

inhaled anesthetics and, 107
Vessels, of elderly patients, 923
VGSCs. *See* Voltage-gated sodium channels
Vinca alkaloids, 833*t*, 845–846
Vinyl halide nephrotoxicity, with inhaled anesthetics, 136, 136*f*
VIP. *See* Vasoactive intestinal peptide
Viral reactivation, neuraxial opioids and, 237
Visceral pain, 202, 203*f*
Vision, 72–74
field of, 73
Horner syndrome, 74
intraocular pressure, 72
lens, 72, 72*f*
pupil, 72, 72*f*
retina, 72–73, 72*f*
visual pathway, 73, 73*f*
Visual cortex, 60
Visual evoked potentials, 70
Vitamin A (retinol, retinoic acid), 740*t*, 745–746, 745*f*
Vitamin B₁ (thiamine), 739–741, 740*t*, 741*f*
Vitamin B₂ (riboflavin), 740*t*, 741–742, 741*f*
Vitamin B₃ (nicotinic acid, niacin), 740*t*, 741*f*, 742
Vitamin B₆ (pyridoxine), 740*t*, 741*f*, 742
Vitamin B₁₂ (cyanocobalamin, cobalamin), 740*t*, 741*f*, 743
Vitamin C (ascorbic acid), 740*t*, 741*f*, 744–745
Vitamin D (calciferol), 740*t*, 745*f*, 746–747
Vitamin E (α -tocopherol), 740*t*, 745*f*, 747
Vitamin K, 740*t*, 745*f*, 747–748
Vitamin K antagonists, 664–666, 665*t*
Vitamins, 739–748
fat-soluble, 740*t*, 745–748, 745*f*
water-soluble, 739–745, 740*t*, 741*f*
VMA. *See* Vanillylmandelic acid
Volatile anesthetics
airway and, 600–601, 600*t*
pulmonary circulation and, 603
Voltage-gated calcium channels, 53*f*, 59, 59*f*
neuronal, 250
Voltage-gated ion channels, 55–57
inhaled anesthetics and, 114
Voltage-gated sodium channels (VGSCs)
blocking of, 264, 266*f*
inhaled anesthetics and, 115
local anesthetics and, 273–274, 276*f*
non- γ -aminobutyric acid sedative-hypnotics and, 177
Vomiting, 75–76, 75*f*, 693. *See also* Postoperative nausea and vomiting (PONV)
opioids and, 212–213
with PCA, 250
von Willebrand factor, 644–645
VTE. *See* Venous thromboembolism

W

- Water-soluble vitamins, 739–745, 740*t*, 741*f*
- α waves, 68, 68*f*
- β waves, 68, 68*f*
- δ waves, 68–69, 68*f*
- θ waves, 68, 68*f*
- White matter, 64
- Whole blood viscoelastic tests, 633
- Wide complex ventricular rhythm, 521
- Withdrawal
 - of β-adrenergic receptor antagonists, 483
 - from opioids, 214, 214*t*, 229
- Work of breathing, 573–574

Z

- Zero-order processes, 25–26, 26*f*
- Zinc, in intravenous fluids, 447
- Zona fasciculata, 759
- Zona glomerulosa, 759
- Zona reticularis, 759
- Zymogens, 627