

Fig. 22.29 Schematic of the Dräger DIVA vaporizer (Drägerwerk AG & Co. KGaA. Diagram reprinted with permission). The vaporizer consists of two modules: an interchangeable vaporizing module, and a gas supply module that is part of the anesthesia workstation. The vaporizing module includes a reservoir for liquid agent and a dosing chamber. The gas supply module consists of a feedback control unit that provides dosing pressure and control, as well as a system of valves. The valves may target vapor injection into either a mixing chamber (to mix with fresh gas flow) or directly into the breathing system (injection independent of fresh gas flow). See text for details.

low-resistance to gas flow, and (3) gas flow that is driven by negative downstream pressure (typically arising from the patient's respiratory effort, but potentially from a bellows or compressible bag). For a more thorough discussion of draw-over anesthesia technique in resource-limited settings, please see Chapter 2, Section 3. The basic design principles are worth a brief illustration.

The *Oxford Miniature Vaporizer* (OMV) is a stainless steel, variable-bypass, draw-over vaporizer that has been in use since 1968 and is particularly popular in the British Armed Forces.^{121e} It has a robust, simple, and portable design and holds up to 50 mL of liquid anesthetic.^{69b} A calibrated dial controls flow through an aperture between a slide valve and obturator located in the bypass chamber (Fig. 22.30).^{121f} Closing the aperture directs more flow into the vaporizing chamber and increases output. Metal mesh wicks increase the surface area for vaporization yet add little resistance to gas flow. The OMV is not temperature compensated and output varies significantly with ambient temperature.^{121g} It does feature a heat sink of water and ethylene glycol ("anti-freeze") housed in the base to resist temperature swings. The OMV is not agent-specific, and different calibrated dials are available for halothane, isoflurane, and sevoflurane.⁴⁴ In order to deliver sufficient sevoflurane concentration for an inhaled induction, two OMVs must be used in series.^{121h} Recently, the *Diamedica Draw-Over Vaporizer* (DDV) has been developed. Although similar in design to the OMV, the DDV tends to deliver more accurate results across a range of dial settings and ambient temperatures.^{69a} It also has a larger reservoir (150 mL) for liquid agent and is available in two versions (halothane/isoflurane and sevoflurane).¹²¹ⁱ

Volatile Anesthetic Reflectors: AnaConDa and Similar Devices. There has been a resurgence of interest in providing inhaled volatile anesthetics to patients in locations outside of the operating room, such as the ICU, where commercial anesthesia workstations are not readily

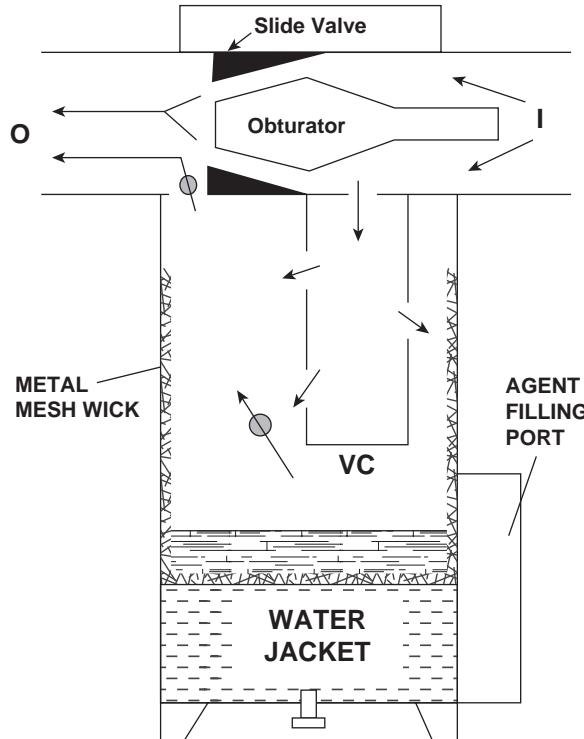


Fig. 22.30 Oxford miniature vaporizer. Gas flows from the inlet, *I*, through a slide valve and towards the outlet, *O*. A dial controls motion of an obturator that diverts flow to the vaporizing chamber, *VC*, and determines vaporizer output. (Redrawn from Dhulkhed V, Shetti A, Naik S, et al. Vapourisers: physical principles and classification. *Ind J Anaesth*. 2013;57[5]:455–419.)

available.^{121j} Indications for ICU delivery of volatile anesthetics include refractory bronchospasm and status epilepticus (see also Chapter 79), as well as a potential alternative to intravenous sedation.^{121k} Barriers to providing volatile anesthesia in the intensive care setting include (1) rapid

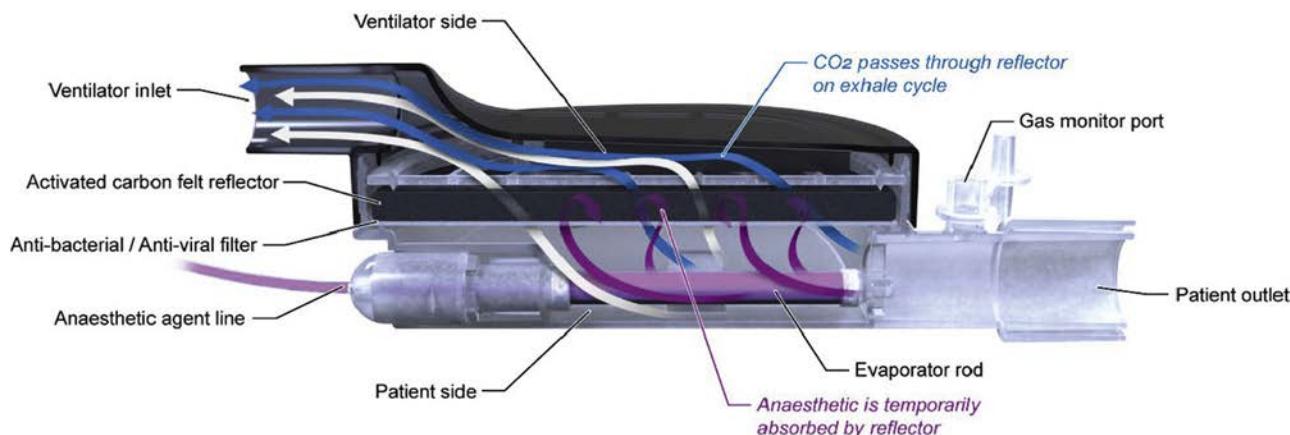


Fig. 22.31 Anesthetic conserving device (AnaConDa) showing the flow of gas during exhalation. (From Farrell R, Oomen G, Carey P. A technical review of the history, development and performance of the anaesthetic conserving device "AnaConDa" for delivering volatile anaesthetic in intensive and postoperative critical care. *J Clin Monitor Comput*. 2018;32[4]:595–604.)

consumption of volatile anesthetics due to the high gas flow rates of modern ICU ventilators, and (2) environmental safety and occupational health hazards due to atmospheric contamination and ineffective scavenging of waste gases.

One possible solution for ICU delivery of volatile anesthetics are reflector-style devices such as the *anesthetic conserving device* (AnaConDa) and *Mirus* device.^{121l,121m} The AnaConDa is a single-use device based on a heat and moisture exchanger (HME) filter and does not require a power source or an anesthesia workstation (Fig. 22.31).¹²¹ⁿ Liquid volatile anesthetic (either isoflurane or sevoflurane) is injected into the device using a standard syringe pump and vaporized through a porous evaporator rod. The patient breathes in the anesthetic vapor normally. Upon exhalation, the breathing gases pass through several layers of filter. The first is an antimicrobial layer typical of HME filters. The second layer is activated carbon that rapidly adsorbs exhaled volatile anesthetic with high efficiency, while CO₂ and other exhaled gases pass through. Upon the next inspiratory cycle, the adsorbed volatile anesthetic molecules are released from the carbon filter and "reflected" towards the patient for re-breathing. The efficiency of the device is approximately 90%, with only 10% loss of vapor passing through the reflector to the ventilator waste gases. A gas sampling port allows for monitoring of end-tidal volatile agent concentration and titration of the syringe pump infusion rate. The Mirus device works on a similar concept, but is capable of delivering desflurane, and incorporates automatic control of end-tidal concentrations.^{121l}

ANESTHETIC BREATHING CIRCUITS

Fresh gas departs from the supply system and enters the anesthetic breathing circuit through the fresh gas line. The functions of the breathing circuit are to deliver oxygen and other gases to the patient and to eliminate CO₂. The breathing system must contain a low-resistance conduit for gas flow, a reservoir that can meet the patient's inspiratory flow demand, and an expiratory port or valve to vent excess gas.¹²² Beyond these fundamentals, circuits are categorized as those that use an absorber to eliminate CO₂ (the circle system) and those that do not (the

Mapleson circuits).¹²³ Circle systems are the most common breathing circuits used for anesthetic delivery. However, certain Mapleson systems are used in anesthesia workstations, particularly in pediatrics, and they are often used by anesthesia providers during transport of patients, procedural sedation, liberation from tracheal intubation (the T-piece), and preoxygenation during out-of-the-operating-room airway management. Therefore both systems are discussed.

Leaks and obstruction represent the two most important hazards associated with the breathing circuit. Most of the time, these problems can be detected during the pre-use checkout of the workstation. However, a firm understanding of the components and function of the breathing system is critical if one is to perform a proper checkout and troubleshoot acute problems. The operator should also be aware of the various standards and alarms associated with this critical part of the anesthesia workstation.

Circle Breathing Systems

The circle breathing system is so named because it allows circular, unidirectional flow of gas facilitated by one-way valves. For many years, the overall design of the classic circle system changed little. Most anesthesia workstations had circle systems with similar schematics and components (Figs. 22.32–22.34). More recently, however, circle breathing systems have evolved along with the technological complexity of workstations. These changes have resulted from efforts to improve patient safety with features such as integrated fresh gas decoupling during positive-pressure ventilation.

The circle system consists of several essential components, including (1) a fresh gas inflow source, (2) inspiratory and expiratory unidirectional valves, (3) inspiratory and expiratory corrugated tubes, (4) a Y-piece that connects to the patient, (5) an overflow or APL or "pop-off" valve, (6) a reservoir or breathing bag, and (7) a canister containing a CO₂ absorbent (see Fig. 22.32). Several additional components are added to enhance patient safety, including a circuit pressure sensor, a pressure gauge, an expiratory (and possibly an inspiratory) flow sensor, and an inspired oxygen concentration sensor. A separate positive end-expiratory pressure (PEEP) valve may be present. Circle

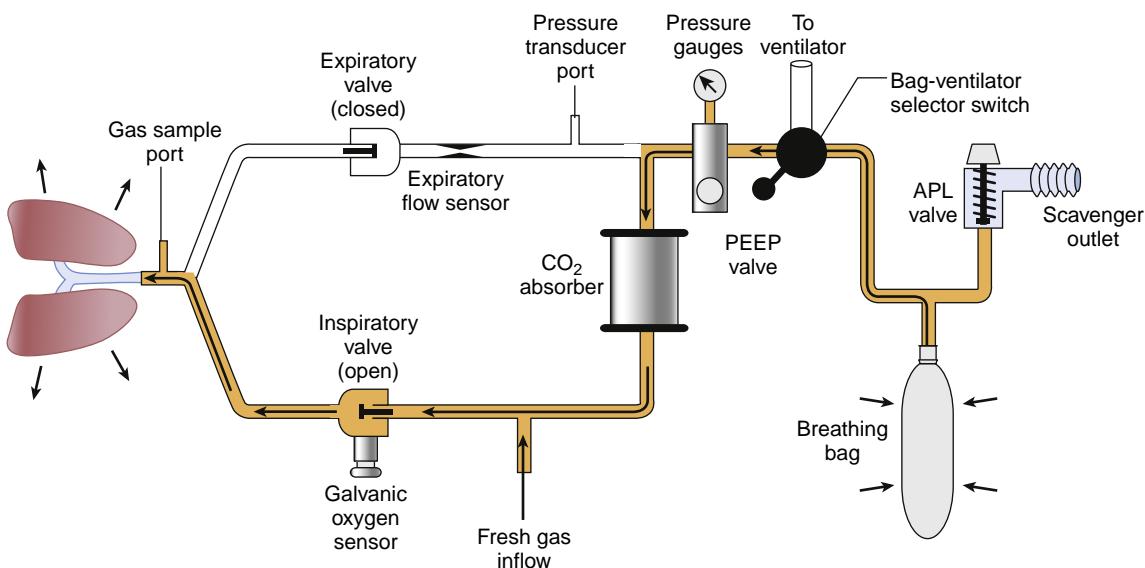


Fig. 22.32 Classic circle breathing system. Spontaneous breathing-inspiratory phase (ventilator not shown). Gas is drawn by the patient from the breathing bag and through the carbon dioxide (CO_2) absorber. It is then mixed with the fresh gas inflow from the gas supply system, traverses the inspiratory valve, and flows to the patient. The expiratory valve prevents rebreathing by not allowing flow to bypass the CO_2 absorber. *APL*, Adjustable pressure-limiting; *PEEP*, positive end-expiratory pressure. (Courtesy Dr. Michael A. Olympio; modified with his permission.)

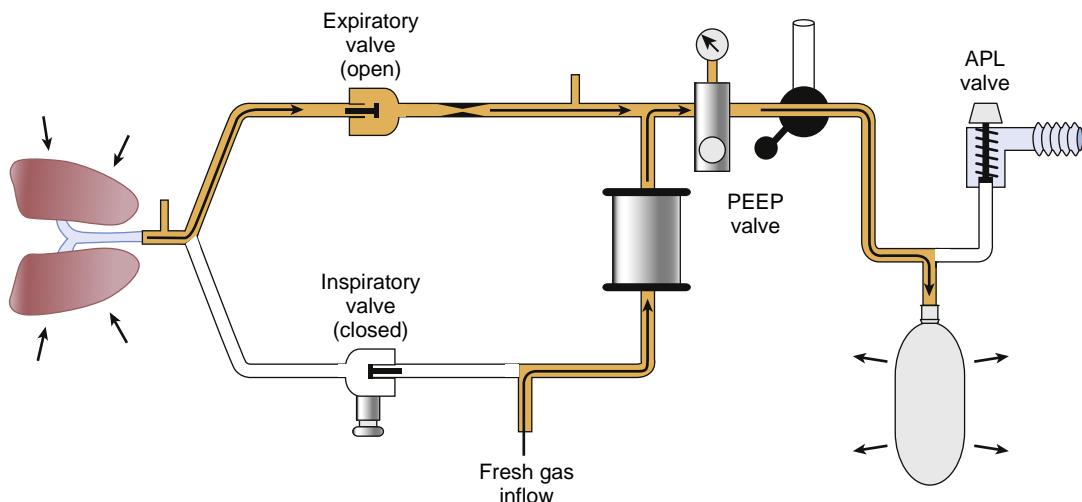


Fig. 22.33 Spontaneous breathing: early expiratory phase. The inspiratory unidirectional valve ensures that all exhaled carbon dioxide (CO_2)-containing gas flows toward the breathing bag and adjustable pressure-limiting (APL) valve before being scrubbed of CO_2 . Fresh gas continues to flow, but now in retrograde fashion, and combines with the exhaled breath. The APL valve remains closed in this example because circuit pressure is still lower than the practitioner-set APL valve pressure threshold (i.e., 10 cm H_2O). *PEEP*, Positive end-expiratory pressure. (Courtesy Dr. Michael A. Olympio; modified with his permission.)

systems must allow for spontaneous ventilation, manual ventilation, and positive-pressure mechanical ventilation, and therefore must function with both the anesthesia reservoir bag and ventilator. The fresh gas inflow enters the circle by a connection from the common gas outlet of the anesthesia machine.

Some of the main advantages of the circle system include (1) maintenance of relatively stable inspired gas concentrations; (2) conservation of respiratory heat and moisture, and anesthetic gases; (3) elimination of CO_2 ; and (4) prevention of operating room pollution. The capability to rebreathe exhaled gases is a unique aspect of circle systems as compared with ICU ventilators. Carbon dioxide is efficiently removed to allow safe rebreathing of

exhaled gases. Waste gas, which is composed of excess carrier gas, anesthetic agent, and CO_2 , is scavenged and eliminated.

Circle breathing systems have several disadvantages. First, they have a complex design that may consist of ten or more individual connections. These multiple links set the stage for misconnections, disconnections, obstructions, and leaks. In a closed-claim analysis of adverse anesthetic outcomes arising from gas delivery equipment, 39% of malpractice claims resulted from breathing circuit misconnections or disconnection.¹²⁴ Malfunction of unidirectional valves can be life-threatening. The circle breathing system is large and compliant when compared with the Mapleson systems, and this property may compromise tidal volume

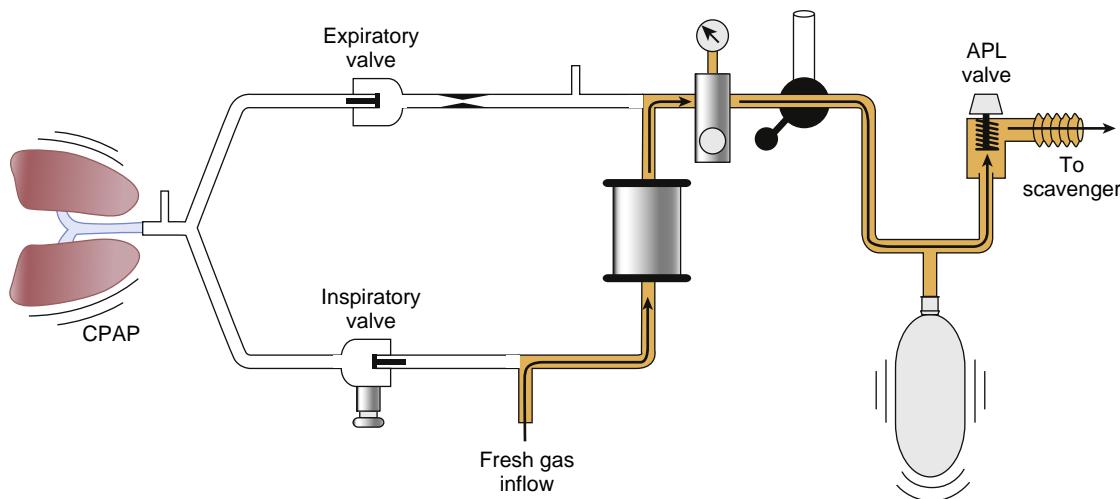


Fig. 22.34 Spontaneous breathing: end-expiratory phase with continuous positive airway pressure (CPAP). Fresh gas continues to flow into the circuit generating pressure that maintains distention of the lungs (CPAP) and the breathing bag. Once the circuit pressure exceeds the adjustable pressure-limiting (APL) valve's set threshold (i.e., 10 cm H₂O), the valve opens, and excess gas flow is vented to the scavenger. (Courtesy Dr. Michael A. Olympio; modified with his permission.)

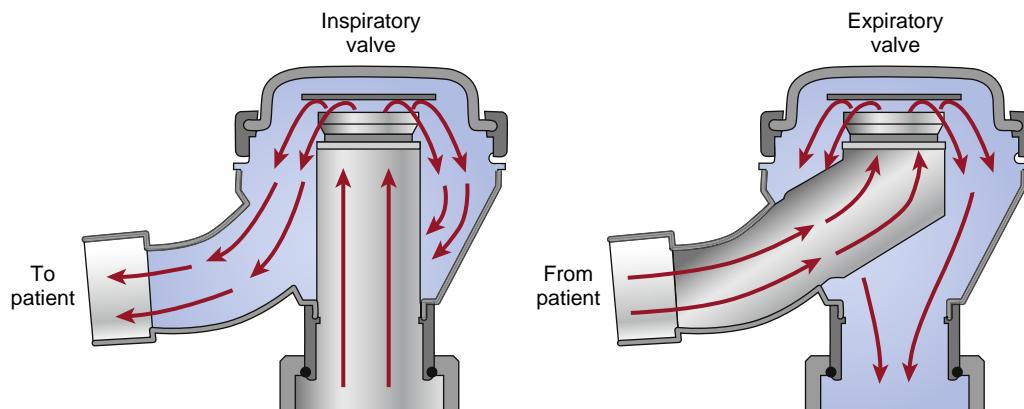


Fig. 22.35 Circle breathing system unidirectional valves. (Modified from Yoder M. Absorbers and breathing systems. In: *Understanding Modern Anesthesia Systems*. Telford, PA: Dräger Medical; 2009:83–126.)

delivery during controlled ventilation. Finally, because circle breathing systems use a CO₂ absorber, anesthetic degradation can occur (see section on carbon dioxide Absorbers).¹²⁵ Specific perils associated with each component of the circle system are discussed in detail in the sections to follow.

Mechanical Components of the Circle Breathing System

Unidirectional Valves. The one-way valves are essential elements of the circle breathing system (Fig. 22.35). They are constructed to resist the humidity that sometimes accumulates in the breathing system. However, these usually reliable valves can occasionally fail during use. The expiratory valve seems to be more vulnerable because it is subject to greater moisture exposure. If a unidirectional valve sticks in the open position, inappropriate rebreathing of CO₂ may occur.^{125a} Capnography may help with diagnosis, as each valve demonstrates a characteristic CO₂ waveform when incompetent.^{126,126a} If the valves are stuck shut, total occlusion of the circuit can result. An expiratory valve stuck in the closed position can lead to barotrauma. Assessing for

proper unidirectional valve function should be part of the anesthesia workstation pre-use check out procedure. Anesthesia machines are constructed so that valve function and motion can either be visibly assessed, or malfunction is indicated by the workstation.¹¹

Adjustable Pressure-Limiting Valve. The APL valve is an operator-adjustable relief valve that vents excess breathing circuit gas to the scavenging system and provides control of the breathing system pressure during spontaneous and manual modes of ventilation. Switching the workstation to a ventilator mode excludes or closes the valve.¹²⁷ Several other common names exist for these devices, including "pop-off" valve and pressure relief valve.¹²² The two basic types of APL valves are the variable-orifice (or variable-resistor) type and the pressure-regulating type. The variable-orifice type functions as a needle valve, much like a flow control valve (Fig. 22.36). The operator adjusts the outlet orifice size, so the resultant breathing system pressure at any given adjustment is directly related to the fresh gas flow rate. Modern machines now mostly use pressure-regulating type APL valves (Fig. 22.37). This type of APL valve has an adjustable

internal spring and an external scale indicating the approximate opening pressure. When the pressure in the system exceeds spring tension, a disk opens and gas is vented (see Fig. 22.37B). Waste gas is prevented from returning from the scavenging system by a downstream check valve. By adjusting spring tension, the operator can choose the desired maximal circuit pressure in manual mode.^{38,122} Unlike variable-orifice type valves, the pressure-regulating APL valves are designed to maintain stable circuit pressure even as fresh gas flow is increased. This type of valve usually has a fully open (to atmosphere) position for spontaneous breathing (see Fig. 22.37C). Continuous positive airway pressure (CPAP) can be more reliably controlled using this type of APL valve.

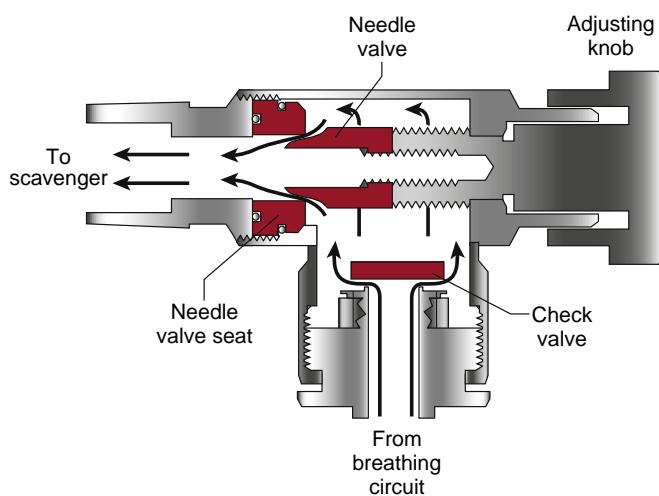


Fig. 22.36 Adjustable pressure-limiting valve: variable orifice type. A weighted check valve prevents gas from flowing backward after being sent to the scavenger. A variable orifice needle valve controls rate of gas egress from the breathing circuit, thereby controlling the circuit pressure. At any given adjusted valve orifice, the pressure in the circuit will depend on the fresh gas flow rate. (Modified from Yoder M. Absorbers and breathing systems. In: *Understanding Modern Anesthesia Systems*. Telford, PA: Dräger Medical; 2009:83–126.)

While APL valves are designed as a safety feature to allow precise control of circuit pressures during manual ventilation, problems do occur. A comparison of two modern anesthesia machines demonstrated that not all APL valves have equivalent linear behavior, and with certain valves the PIPs may routinely exceed set values.^{127a} This serves as a reminder that the operator must vigilantly monitor circuit pressure during manual ventilation. Mechanical failures of APL valves have been reported due to breakage or trapping of gas sampling lines under the edge of the control knob.^{127b,127c}

Anesthesia Reservoir Bag or “Breathing Bag.” The anesthesia reservoir bag, or “breathing bag,” provides several important functions, including (1) serving as a reservoir for exhaled gas and excess fresh gas, (2) providing a means of delivering manual ventilation or assisting spontaneous breathing, (3) serving as a visual or tactile means of monitoring a patient’s spontaneous breathing efforts, and (4) partially protecting the patient from excessive positive pressure in the breathing system, such as in the case of inadvertent closure of the APL valve or an obstruction of the scavenge line [Fig. 22.38A]). Standard adult breathing bags have a nominal volume of 3 L; pediatric bags are available as small as 0.5 L. The reservoir bag is the most compliant part of the breathing system. The pressure-volume characteristics of standard bags are such that they inflate to a maximal pressure, and then slightly decrease to a plateau as filling continues to higher volumes (Fig. 22.38B).^{122,128,129,129a} Anesthesia reservoir bags must adhere to pressure standards, which mandate a minimum pressure of approximately 30 cm H₂O and a maximum pressure of approximately 60 cm H₂O when the bag is filled to four times its stated capacity.¹³⁰ Although most bags adhere to these standards, some latex-free bags have exceeded the upper pressure limit.¹²⁹ Classically, the reservoir bag was excluded from the breathing circuit when the ventilator was in use. However, on most contemporary Dräger workstations,

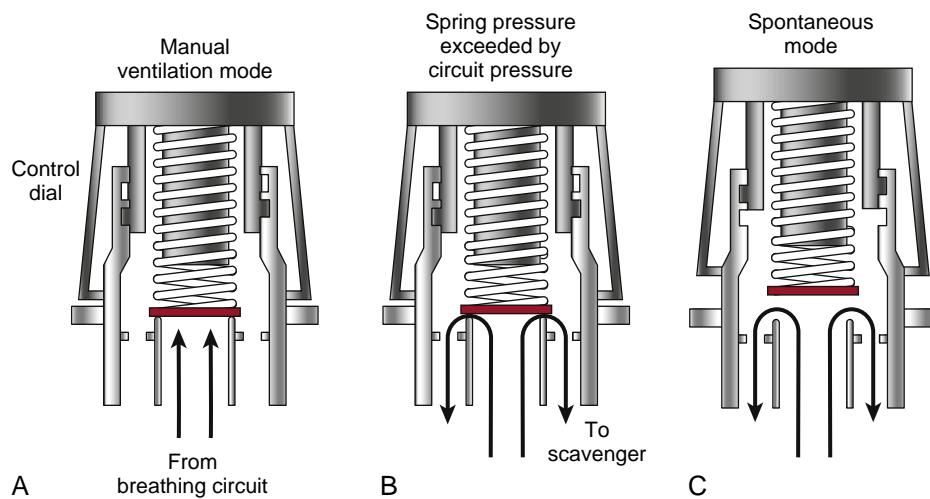
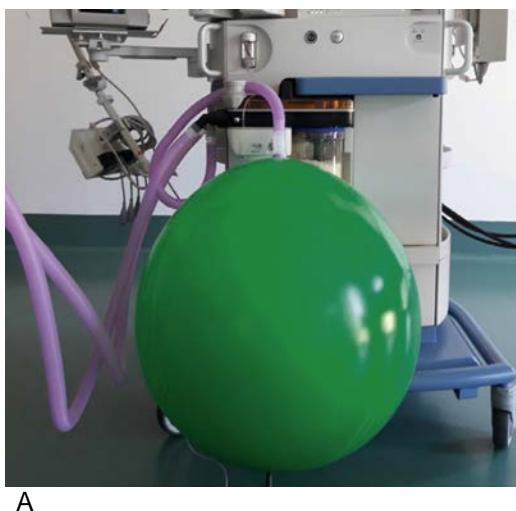
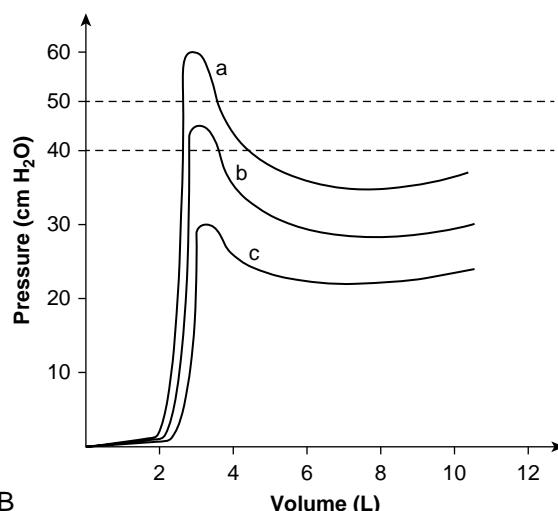


Fig. 22.37 Adjustable pressure-limiting valve: pressure-regulating type. (A) In the “manual” setting, the operator adjusts spring tension, thereby adjusting valve opening pressure. In this image the breathing circuit pressure has not yet exceeded spring tension. (B) Breathing circuit pressure has exceeded the set pressure (spring tension), and gas is vented to the scavenger. With the pressure regulating type of adjustable pressure-limiting valve, circuit pressure is independent of the fresh gas flow rate. (C) When the valve is placed in the spontaneous mode, the disk is lifted off the valve seat, and gas flows freely to the scavenger. A check valve downstream prevents waste gas from returning to the breathing circuit.



A



B

Fig. 22.38 Safety function of the breathing circuit reservoir bag when overdistended. The standard for reservoir bags is that the maximum pressure should not exceed approximately 60 cm H₂O at four times the stated capacity.¹³⁰ However, the pressure inside many reservoir bags peaks at a lower volume, and all should maintain a plateau pressure with further expansion.¹²⁸ (A) A breathing bag distended to a diameter of ~66 cm and volume of ~150 L. The pressure inside the bag is 34 cm H₂O. (B) Pressure versus volume filling curves for three different reservoir bags demonstrating a peak and plateau pressure. Vigilance should prevent overfilling from occurring because the continuing positive pressure alarm should be sounding while the bag is inflating. (From Križmarčić M. Functions of anesthesia reservoir bag in a breathing system. *Slov Med J.* 2017;86:226–235.)

the reservoir bag is integral to circuit function during mechanical ventilation, where it serves as an exhaled and fresh gas reservoir.^{31b,38,131,131a}

Corrugated Breathing Circuit Tubing. The breathing circuit tubing, which accounts for most of the volume within the circle system, has certain vulnerabilities. First, these circuits are compliant, and some of the volume intended for delivery to the patient during positive-pressure ventilation is lost to distention of the tubing. Many modern anesthesia workstations perform a compliance test to compensate for this effect. Alternatively, the workstation may compensate for discrepancies in the set versus delivered tidal volume. It is important that these tests be performed with the actual circuit that is to be used for anesthesia delivery. For instance, if a circuit extension is to be used to facilitate turning the operating room table 180 degrees, the compliance, leak, and flow tests should be performed with the extension in place. Circuit tubing may also be a source of leaks or obstruction (see below).

Y-Piece. The Y-piece is the distal (nearest the patient) part of the circuit that merges the inspiratory and expiratory limbs. It has a 15-mm inner diameter to connect to an endotracheal tube or elbow connector, and a 22-mm outer diameter to connect to a face mask. The dead space in the circle breathing system begins at the Y-piece and continues to the patient (i.e., the portions of the circuit with bidirectional gas flow, compare Figs. 22.32 and 22.33).^{131b} On modern anesthesia machines, the gas sampling port is located at or near the Y-piece to allow monitoring of both inspiratory and expiratory gases.

Filters and Heat and Moisture Exchangers. The use of HMEs and filters within the anesthesia breathing circuit is common. HMEs help replace the normal warming and humidifying function of the upper airway, which is often

bypassed by an artificial airway during anesthesia.¹³² Filters are used to prevent the transmission of microbes from the patient to the machine and hence potentially to other patients. No consensus agreement pertaining to their use exists. Current ASA recommendations endorse the use of filters only in the context of patients with tuberculosis.¹³³ If a filter is to be used for this purpose, it should have an efficiency rating higher than 95% for particle sizes larger than 0.3 µm. The filter should be placed between the endotracheal tube and the Y-piece.¹³⁴

Sensors

Inspired Oxygen Concentration Monitor. The ASTM standards state that the workstation must be equipped with a sensor to monitor the oxygen concentration in the inspiratory limb or at the Y-piece of the breathing circuit. A low oxygen concentration alarm must sound within 30 seconds if the fraction of inspired oxygen (FiO₂) drops below a set limit, which cannot be adjustable to less than 18% v/v%.²⁰ The oxygen sensor is truly the patient's last line of defense from receiving a hypoxic gas mixture. *Galvanic cell oxygen analyzers* are often used for this purpose, but they have a finite life span and are prone to drift.^{134a} They therefore require daily calibration during the workstation pre-use check. A common location for galvanic sensors is in the housing of the inspiratory unidirectional valve (see Fig. 22.32). Modern anesthesia workstations (e.g., Dräger Apollo) increasingly use *side-stream multigas analyzers* at the Y-piece as the exclusive inspiratory oxygen monitor.^{131a,134c} *Paramagnetic oxygen analyzers*, which require less frequent calibration, are typically used in these monitors.

Flow Sensors. Flow sensors are used on the anesthesia machine primarily to measure tidal volume. The workstation must have a device that monitors the patient's exhaled tidal volume, minute ventilation, or both.¹¹ These sensors may also be used to display flow waveforms and/or flow-volume loops. Finally, some workstations use flow sensor

measurements as a feedback signal to maintain stable tidal volume delivery at varying fresh gas flow rates. Although early flow sensors were usually mechanical respirometers, contemporary machines may use differential pressure sensors, heated-wire anemometers, ultrasonic flow sensors, or variable-orifice flow sensors. The location of the flow sensor can vary, but a sensor for exhaled gas flow is required at a minimum.

Breathing Circuit Pressure Sensors. The continuous measurement of airway pressure in the breathing circuit is critical to patient safety. Several requirements must be met. First, anesthesia workstations must continuously display pressure in the breathing system. Second, operator-adjustable alarms must be present for *high pressure* as well as for *continuous positive pressure* lasting 15 seconds or longer. Excessive high pressure or prolonged positive airway pressure can compromise venous return, decrease cardiac output, interfere with ventilation, or cause barotrauma. An alarm must also sound if *negative pressure below $-10\text{ cm H}_2\text{O}$* occurs in the breathing circuit for more than 1 second. Finally, when automatic ventilation is in use, the machine must alarm whenever the breathing pressure falls below a preset or adjustable *threshold pressure* for more than 20 seconds. This alarm may serve as a disconnection alarm, but low-volume or exhaled CO_2 monitoring may also be used (see below).¹¹ The location of pressure sensors in the breathing system varies. They are often located in the nondisposable portion of either the inspiratory or expiratory limb near one of the unidirectional valves.^{134b} Dräger machines transduce pressure from the CO_2 absorber system.^{131a} It is important to remember that the breathing circuit pressure may not accurately represent the patient's airway pressure, especially if the pressure sensor is located far from the Y-piece.^{134b} Older machines have a mechanical pressure gauge, while newer models may display a digital representation of this gauge.

Circle System Function—Semiclosed, Semiopen, and Closed Systems. Circle system function is illustrated in Figs. 22.32–22.34. The extent of rebreathing, and therefore the conservation of exhaled gases, depends on the fresh gas flow rate. Higher fresh gas flow rates result in less rebreathing and greater waste gas. Contemporary circle systems are usually operated in a *semiclosed* manner, meaning that some rebreathing occurs, but some waste flow is vented through the APL or waste gas valve of the ventilator. The delivery of *low-flow* anesthesia ($\leq 1.0\text{ L/min}$ fresh gas flow) with a circle system exemplifies a *semiclosed* system. *Low-flow* anesthesia generally refers to a technique where fresh gas flow is less than minute ventilation, and at least 50% of expired gas is rebreathed after carbon dioxide removal.^{131b}

A circle system operated in a *semiopen* manner implies a higher fresh gas flow rate with minimal rebreathing and more venting of waste gas. The advantages of conducting *low-flow* or *minimal-flow* ($\leq 0.5\text{ L/min}$) anesthesia include the decreased use of volatile anesthetic agents, improved temperature and humidity control, and reduced environmental pollution. The disadvantages include difficulty in rapidly adjusting anesthetic depth and the theoretical possibility of accumulating unwanted exhaled gases (e.g., carbon monoxide, acetone, methane) or volatile anesthetic

degradation products (e.g., compound A, carbon monoxide—see section on carbon dioxide absorbers later).¹³⁵

A *closed* system is one in which the rate of oxygen inflow exactly matches metabolic demand, rebreathing is complete, and no waste gas is vented. A volatile anesthetic agent is added to the breathing circuit in liquid form in precise amounts or is initially introduced through the vaporizer.¹³⁶ Closed-circuit anesthesia maximizes the advantages of *low-* and *minimal-flow* anesthesia. However, the vigilance demanded by this technique make it impractical for routine use with contemporary equipment; thus it is rarely employed.¹³⁷

Potential Circle System Problems

LEAKS AND DISCONNECTIONS. Breathing circuit leaks and disconnections continue to cause critical incidents in anesthesia.¹⁴⁰ Common sources of leaks include disposable tubing and components, as well as points of connection within the breathing circuit and at the CO_2 absorber canister.¹⁴¹ Although leaks can develop during the course of anesthesia, such as a partial disconnection, most can be detected during a thorough workstation pre-use checkout. Leaks can be small, and easily overcome by increasing fresh gas flow to compensate for lost volume, or they can be very large and render ventilation impossible. No matter the size, *all leaks should be investigated*. Several monitors can assist the anesthesia provider in detecting a leak or circuit disconnection during the course of anesthetic care (Table 22.7).

Breathing circuit pressure monitoring is an extremely important aid in diagnosing leaks and disconnections. As discussed earlier, breathing circuit pressure monitoring is a required feature of anesthesia workstations. The *threshold pressure* (or *low peak inspiratory pressure*) alarm is useful for detecting leaks and disconnections. When using a controlled ventilation mode, an audible and visual alarm is generated if the breathing system pressure drops below the threshold limit for more than 20 seconds (Fig. 22.39A). Visual alarm examples include "Apnea Pressure," "Check Breathing Circuit," and "Low Pressure."^{38,141a,141b} The specific times required before sounding the alarm may vary slightly between machines. The *threshold pressure alarm* limit is operator-adjustable on some machines, and may also have an "autoset" feature that applies an algorithm to set an appropriate limit based on current airway pressures.^{131,141c} As can be seen in Fig. 22.39B, setting the threshold limit too low may allow a partial disconnection (leak) to go unrecognized. Conversely, setting the threshold limit too high can result in an erroneous alarm.

Respiratory volume monitors (flow sensors) are useful in detecting leaks or disconnections. Low exhaled tidal volume and/or low minute ventilation alarms may first alert the operator to these problems. The user should bracket the minute ventilation alarms slightly higher and lower than the patient's requirements. An autoset feature may be available for minute ventilation monitoring as well.¹³¹ Some workstations will alarm if a significant disparity exists between inhaled and exhaled tidal volumes, or when the measured tidal volume does not achieve the set tidal volume.¹⁴²

Finally, all modern workstations have integrated gas monitoring with alarms for *exhaled CO_2* . Total loss of the

TABLE 22.7 Methods of Detecting Leaks and Disconnections During the Course of Anesthesia

Method	Leak Indications
Breathing circuit pressure sensors	<i>Threshold pressure alarm*</i> Pressure waveform evaluation Trend of peak pressures
Workstation tidal volume sensors	Low minute ventilation or low tidal volume alarm Failure to deliver set tidal volume Disparity between inhaled and exhaled tidal volumes Decreasing trend of tidal volume and minute ventilation
Exhaled gas analysis	Exhaled carbon dioxide automated monitoring Abnormal appearance and trend of capnography tracing
Physiologic sensors (e.g., SpO_2 , HR, BP)	<i>Late detection</i> of significant leaks and disconnections because the patient is already decompensating
A vigilant practitioner	Assesses breath sounds and chest wall excursion Pays close attention to alarms and responds promptly Observes workstation and physiologic monitors Notes that ventilator bellows is not refilling completely and tidal volumes are decreasing Notes that flow rate requirements are increasing to refill an ascending bellows Senses that breathing bag motion and feel are not normal Detects the odor of anesthetic gas Follows his or her instinct that something is not right

*ISO standard.

BP, Blood pressure; HR, heart rate; SpO_2 , saturation of peripheral oxygen.

capnogram should alert the operator to a loss of ventilation and possible circuit disconnect. More subtle changes in capnogram amplitude or waveform may indicate a leak.

MISCONNECTIONS. Unfortunately, misconnections of the breathing system are not rare. Anesthesia workstations, breathing systems, ventilators, and scavenging systems incorporate many diameter-specific connections. Despite the efforts of standards committees to assign different diameters to various circuit connections, misconnections continue to occur. The ingenuity of some individuals in outwitting these “foolproof” systems has led to various hoses being adapted or forcefully fitted to inappropriate terminals, and even to various other solid cylindrical protrusions of the anesthesia machine.^{143,144} Operators and technicians should be properly trained on their respective workstations and modifications should be discouraged.

OBSTRUCTION. Occlusion (obstruction) of the breathing circuit may occur and can have severe consequences. Tracheal tubes may kink. Breathing circuit valves or other components can malfunction. Hoses throughout the breathing circuit are subject to occlusion by internal obstruction or external mechanical forces that can impinge on flow. Blockage of HMEs by secretions can also cause significant obstruction.¹⁴⁵ Case reports describe bilateral tension pneumothorax caused by blockage of a bacterial filter in the expiratory limb,¹⁴⁶ or a misplaced disk in an expiratory valve.¹⁴⁷ Because retained CO_2 absorber canister wrappings have caused circuit obstruction, ASTM standards now require that absorbers be packaged in a way that immediately identifies the presence of a wrapper.^{127,148,149} Defects associated with disposable circuit components or the tubing itself have caused severe circuit obstruction and sometimes injury to the patient.¹⁵⁰⁻¹⁵⁴ Misplaced Luer caps have made their way into the elbow connector of the circuit because of packaging or processing and have caused obstruction.^{155,156} Incorrect insertion of flow direction-sensitive components

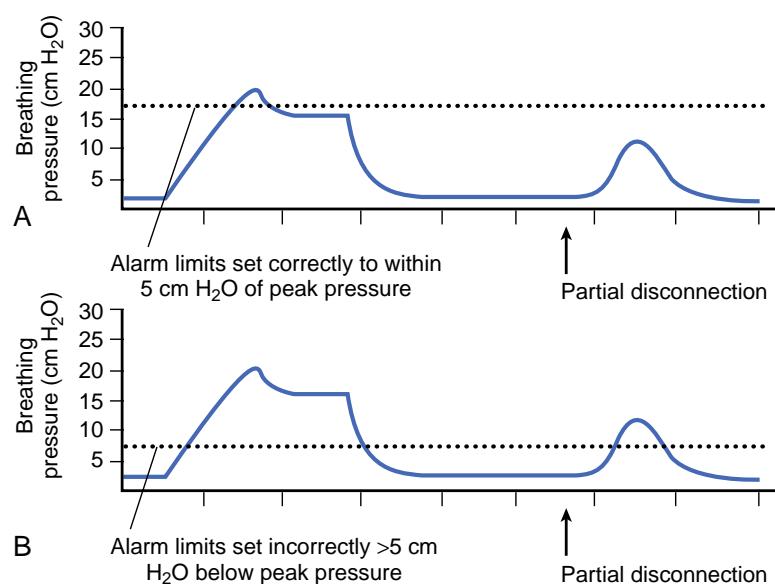


Fig. 22.39 Threshold pressure alarm limit. (A) The threshold pressure alarm limit (dotted line) has been set appropriately. An alarm is actuated when partial disconnection occurs (arrow) because the threshold pressure alarm limit is not exceeded by the breathing circuit pressure. (B) Partial disconnection is unrecognized by the pressure monitor because the threshold pressure alarm limit has been set too low. (Redrawn from North American Dräger. *Baromed Breathing Pressure Monitor: Operator's Instruction Manual*. Telford, PA: North American Dräger; 1986.)

can result in a no-flow state. Examples of these components include some older PEEP valves and cascade humidifiers. Only the performance of a manual circuit flow test, or a similar automated test, during the pre-use checkout will reliably detect an obstruction. *If you are struggling to ventilate a patient and are unsure why, do not delay in switching to a self-inflating resuscitation bag.* Ventilate the patient first, troubleshoot later.

Variations in Circle Breathing System Design. Numerous variations of the circle system are possible, depending on the relative positions of the unidirectional valves, the APL valve, the reservoir bag, the CO₂ absorber, and the site of fresh gas entry. However, to prevent rebreathing of CO₂ in a traditional circle system, three rules must be followed: (1) a unidirectional valve must be located between the patient and the reservoir bag on both the inspiratory and expiratory limbs, (2) the fresh gas inflow cannot enter the circuit between the expiratory valve and the patient, and (3) the APL valve cannot be located between the patient and the inspiratory valve. If these rules are followed, any arrangement of the other components will prevent rebreathing of CO₂.¹²⁵ Design departures from the traditional circle breathing system are becoming more common as workstations evolve. Some of these designs are driven by strategies to eliminate the impact of varying fresh gas flow rates or oxygen flush on inspiratory tidal volume and airway pressure during mechanical ventilations (fresh gas decoupling or compensation). These variations are addressed later, in section on anesthesia ventilators.

Carbon Dioxide Absorbers

Circle breathing systems require a means of CO₂ removal from the exhaled gases to avoid rebreathing and hypercapnia. Although increasing the fresh gas inflow to high levels can dilute out most CO₂ in the circle system, this is a very inefficient way to conduct an anesthetic. Because typical gas flows through the anesthesia machine are less than minute ventilation (*semiclosed* system), absorption of CO₂ is essential. If one could design an ideal CO₂ absorber, its characteristics would include a lack of reactivity with common anesthetics, an absence of toxicity, low resistance to airflow, minimal dust production, low cost, ease of handling, and high efficiency. It should also be easy to assess for absorber depletion (i.e., a diminished ability to remove CO₂). Finally, the container that houses the absorber should be easy to remove and replace, should maintain breathing circuit integrity if quickly replaced during use, and should impose minimal risk of causing breathing system leaks or obstruction. Carbon dioxide absorbers are not unique to anesthesiology. They are also used in certain military and commercial diving equipment, submarines, space operations, mining and rescue operations, and hyperbaric facilities. In these environments, CO₂ absorbers are often referred to as CO₂ *scrubbers*.

Absorber Canister. Although CO₂ absorber canister configurations vary, they must be visible to the operator and transparent to monitor for absorber presence and color. On traditional anesthesia machines, the absorber consists of a single clear plastic canister (or two canisters arranged in series). Opening a traditional canister assembly abolishes

the integrity of the breathing circuit. If the absorber needs to be changed in the course of anesthesia, and apnea cannot be tolerated, it is necessary to ventilate by other means. These older canisters are a common source of leaks due to their multiple components and compression assembly method.¹⁴¹ The canisters are filled either with loose bulk absorbent or with factory-supplied disposable cartridges called *prepacks*. Loose granules from bulk absorbent may lodge between the canister and the O-ring gasket of the absorber and create a clinically significant leak. Leaks have also been caused by defective prepacks or those that were larger than factory specifications.^{154,157} Prepacks can also cause total obstruction of the circle system if the clear plastic shipping wrapper is not removed before use.¹⁴⁸ Problems with rebreathing CO₂ have been caused by canister apparatus reassembly issues.¹⁵⁸⁻¹⁶⁰

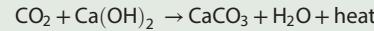
Many modern workstations now use single canister absorbers that are disposable and easily replaceable. Increasingly, workstation design allows the canister to be replaced during anesthesia without interfering with breathing system integrity, sometimes referred to as a *bypass* feature.^{141a} A potential risk imposed by this feature is that the machine may pass an automated or manual leak test *without* the absorber attached.

Chemistry of Absorbents. Carbon dioxide is removed from the breathing circuit through absorption by chemicals within the absorber canister. Through a series of reactions, CO₂ is transformed into water, heat, and other byproducts through a chemical process that neutralizes an acid (CO₂ or carbonic acid) with one or more basic compounds. Most absorbents use calcium hydroxide [Ca(OH)₂] to react with the expired CO₂, producing insoluble calcium carbonate (CaCO₃) (Box 22.2). However, because CO₂ does not react quickly with Ca(OH)₂, water and small amounts of stronger base catalysts are required to speed up the reaction. Calcium hydroxide-based absorbents vary in content of water, strong base

BOX 22.2 Carbon Dioxide Absorber Reactions (Net and Sequential)

Carbon Dioxide Reaction With Soda Lime

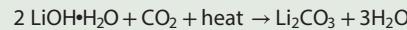
Net Reaction



Sequential Reactions

1. CO₂ (gas) + H₂O (liquid) ⇌ H₂CO₃ (aqueous)
2. H₂CO₃ + 2NaOH (or KOH) → Na₂CO₃ (or K₂CO₃) + 2H₂O + heat
3. Na₂CO₃ (or K₂CO₃) + Ca(OH)₂ → CaCO₃ + 2NaOH* (or KOH*) + heat

Carbon Dioxide Reaction With Lithium Hydroxide Monohydrate



*Note: Sodium hydroxide (NaOH) and potassium hydroxide (KOH) are catalysts in this reaction mechanism (they are neither created nor destroyed). LiOH, Lithium hydroxide.

catalysts (e.g., sodium hydroxide or potassium hydroxide), humectants (e.g., calcium chloride), and hardening agents such as silica. Newer absorbents only have trace amounts of potassium hydroxide (KOH) or sodium hydroxide (NaOH) because these bases have been associated with anesthetic degradation. One absorbent brand replaces $\text{Ca}(\text{OH})_2$ entirely with lithium hydroxide (LiOH), which does not require any additional catalysts to react with CO_2 . Key differences in absorbents include their capacity for CO_2 and their propensity to react with volatile anesthetics and produce potentially harmful degradation products (e.g., carbon monoxide and compound A). The composition of several absorbents is shown in Table 22.8.¹⁶¹⁻¹⁶⁶

Soda lime is a mixture of chemicals that contains about 80% $\text{Ca}(\text{OH})_2$, also known as *slaked lime*, along with water and small amounts of strong base (see Box 22.2). First, CO_2 reacts with liquid water present on and within the absorbent granules to yield carbonic acid (H_2CO_3). This step requires water and explains why all $\text{Ca}(\text{OH})_2$ -based absorbents contain approximately 15% H_2O by mass. Second, the strong base additives NaOH and KOH react quickly with H_2CO_3 to yield the soluble salts sodium carbonate (Na_2CO_3) and potassium carbonate (K_2CO_3). All available active strong base is quickly depleted. Third, the carbonates react with $\text{Ca}(\text{OH})_2$ to yield insoluble CaCO_3 . Note that NaOH and KOH are regenerated in this step and therefore meet the definition of catalysts. Since additional CO_2 cannot dissolve in water until H_2CO_3 is consumed by strong base (step 2), the rate of NaOH and KOH regeneration (step 3) is the rate-limiting step.^{166a} Some CO_2 may react directly with $\text{Ca}(\text{OH})_2$, but as mentioned, this reaction is slower. Byproducts of the entire process are water and heat.^{167,168}

Unlike soda lime and the $\text{Ca}(\text{OH})_2$ -based absorbents, LiOH-based absorbents do not require catalysts. LiOH is a strong base and reacts quickly with CO_2 . Although liquid water is not required to generate carbonic acid as in the

classic $\text{Ca}(\text{OH})_2$ reaction, some water molecules are still required for the CO_2 reaction with LiOH. These water molecules are supplied by humidity in the exhaled breathing gases and combine with the crystal lattice of LiOH in a 1:1 ratio through a process called “hydration.”^{168a} LiOH that does not contain water is referred to as *lithium hydroxide anhydrous*. LiOH chemically bound to water is called *lithium hydroxide monohydrate* ($\text{LiOH} \cdot \text{H}_2\text{O}$). Because the hydration reaction is *exothermic* (gives off heat), absorbents composed of *LiOH anhydrous* generate heat as they extract humidity during use. *LiOH monohydrate*-based absorbents are hydrated at the factory and therefore generate less heat when used in circle breathing systems. Once hydrated, LiOH removes CO_2 from the breathing circuit through an endothermic reaction (absorbs heat) that produces insoluble lithium carbonate (see Box 22.2).

Interactions of Inhaled Anesthetics With Absorbents

FORMATION OF POTENTIALLY HARMFUL DEGRADATION PRODUCTS. Volatile anesthetic agents have long been known to interact with the strong bases (KOH and NaOH) found in $\text{Ca}(\text{OH})_2$ -based absorbents to form degradation products. For historical perspective, trichloroethylene, a volatile anesthetic introduced to clinical use in 1940, was found to be associated with neurologic toxicity (particularly cranial nerve neuropathies and encephalitis).^{169,170} Experimental investigation determined that dichloroacetylene, a toxin, was being formed by a base-catalyzed reaction with prior formulations of soda lime. This reaction was more likely to occur if the soda lime had a high content of strong base and was dry. Today, the main degradation products of concern are compound A, associated with the use of sevoflurane, and carbon monoxide (CO), mainly associated with the use of desflurane, enflurane, and isoflurane.¹⁷¹ Other degradation products include formaldehyde and methanol, but these are not discussed here.¹⁶⁵

TABLE 22.8 Carbon Dioxide Absorber Comparisons

Absorbent (Reference)	$\text{Ca}(\text{OH})_2$ (%)	LiOH (%)	H_2O (%)	NaOH (%)	KOH (%)	Other (%)
Classic soda lime (165)	80	0	16	3	2	—
Baralyme (164)*	73	0	11-16	0.0	5	11 $\text{Ba}(\text{OH})_2$
Sodasorb (161)*	76.5	0	18.9	2.25	2.25	—
Dragersorb 800 Plus (162, 166)*	82	0	16	2	0.003	—
Medisorb (166)*	81	0	18	1-2	0.003	—
New soda lime*	73	0	<19	<4	0	—
Sodasorb LF (163)	>80	0	15-17	<1	0	—
Dragersorb Free (161, 164)	74-82	0	14-18	0.5-2	0	3-5 CaCl_2
Sofnolime*	>75	0	12-19	<3	0	—
Amsorb Plus (161, 165)	>75	0	14.5	0	0	<1 CaCl_2 and CaSO_4
Litholyme*	>75	0	12-19	0	0	<3 LiCl
SpiraLith*	0	≈95	0 [†]	0	0	≤5 PE

*Materials Safety Data Sheets, Occupational Safety and Health Administration, U.S. Department of Labor.

[†]Up to 60% of LiOH is chemically bound 1:1 with H_2O as lithium hydroxide monohydrate (see text for details).

$\text{Ba}(\text{OH})_2$, Barium hydroxide; CaCl_2 , calcium chloride; $\text{Ca}(\text{OH})_2$, calcium hydroxide; CaSO_4 , calcium sulfate; KOH, potassium hydroxide; LiCl , lithium chloride; LiOH, lithium hydroxide; NaOH, sodium hydroxide; PE, polyethylene.

COMPOUND A PRODUCTION. Sevoflurane can undergo a base-catalyzed degradation into fluoromethyl-2,2-difluoro-1-(trifluoromethyl) vinyl ether, known as *compound A*. Compound A is nephrotoxic to rats at concentrations that can occur in the breathing circuit during clinical conditions.^{169,172} Moreover, in a limited number of volunteer studies, sevoflurane was associated with transient albuminuria and glucosuria.^{173,174} To date, however, mounting data show no relationship between sevoflurane use and postoperative renal dysfunction in humans (including patients with preoperative renal insufficiency).^{169,175-180} The sevoflurane package insert states that patient exposure should not exceed 2 MAC-hours at flow rates between 1 and 2 L/min in order to minimize risk from compound A. Flow rates less than 1 L/min are not officially recommended, although these recommendations predate several studies demonstrating safety at lower flow rates.

Several physical factors may predispose to higher concentrations of compound A in the breathing circuit, including the following:

- Low-flow or closed-circuit anesthetic techniques
- Higher concentrations of sevoflurane
- Type of absorbent (KOH or NaOH-containing)
- Higher absorbent temperatures
- Fresh absorbent^{171,172,175,181}

The type and ratio of strong bases within the CO₂ absorbent affects the degree of sevoflurane degradation. KOH seems to cause more breakdown than NaOH.^{164,166} For example, classic soda lime and Baralyme (which was voluntarily withdrawn from the market) both contain significant amounts of KOH and have a greater propensity to generate compound A than newer absorbents (see Table 22.8).¹⁶⁶ LiOH-based absorbents and newer Ca(OH)₂-based absorbents that are free of KOH and NaOH generate zero or negligible amounts of compound A.^{162,163,166,182,182a,182b} Given the safe track record of sevoflurane and ongoing improvements in CO₂ absorbents, it may be concluded that compound A poses minimal risk to patients during routine clinical practice.

CARBON MONOXIDE PRODUCTION. Strong-base containing absorbents that are extremely dry (desiccated) can also degrade inhaled anesthetics to clinically significant concentrations of CO.¹⁶⁴ Under certain conditions, this process can produce blood carboxyhemoglobin levels of 35% or greater in an exposed patient.¹⁸⁴ A typical scenario involving a dangerous CO exposure would be the first case on a Monday morning, after high continuous gas flows had accidentally been left on throughout the weekend and desiccated the absorbent.^{185,186} Machines in remote locations are more frequently found with desiccated absorbent.¹⁸⁶ Prolonged fresh gas flow rates of 5 L/min or greater are sufficient to cause critical drying of the absorbent, especially when the breathing bag is left off the circle system. Because the inspiratory valve leaflet produces some resistance to flow, fresh gas tends to flow retrograde through the absorber and out the breathing bag mount (the path of least resistance). The presence of a breathing bag allows slight pressure build-up that resists this flow (see the classic circle breathing system in Fig. 22.32).¹⁸⁴ Desiccation of absorbent is unlikely to occur during anesthesia delivery since CO₂ absorption produces water (and patients exhale humidified gas).

Several factors increase the production of CO and risk of carboxyhemoglobinemia:

- Inhaled anesthetic used (for a given MAC multiple, the magnitude of carbon monoxide production is desflurane \geq enflurane > isoflurane >> halothane = sevoflurane)
- Degree of desiccation of the absorbent
- Type of absorbent (KOH or NaOH-containing)
- Higher temperature
- Higher concentrations of anesthetic¹⁸⁷
- Low fresh gas flow rates
- Smaller patient size^{188,189}

As with compound A production, the presence of strong bases (KOH and NaOH) in the desiccated absorbent correlates with the propensity to degrade certain anesthetics and liberate CO. Therefore Baralyme (now withdrawn) and to a lesser extent soda lime were more likely to produce CO when desiccated than newer-generation absorbents (see Table 22.8).¹⁹⁰ Omission of NaOH and KOH from the Ca(OH)₂-based absorbents reduces or eliminates the potential to produce CO or compound A without significant impact on the capacity for CO₂ absorption.^{182,191} LiOH absorbent produces essentially no CO and maintains excellent CO₂ absorption.^{162,182b,191a}

ABSORBENT HEAT PRODUCTION. One extremely rare but potentially life-threatening complication related to CO₂ absorbent is the development of extreme exothermic reactions that lead to fires and explosions.¹⁹²⁻¹⁹⁴ Specifically, this seems to occur when desiccated strong base absorbents (particularly Baralyme) interact with sevoflurane. Under experimental conditions, desiccated Baralyme absorbers exceeded 200°C (392°F) and higher, and fire was noted in some of the breathing circuits.¹⁹⁵ The buildup of very high temperatures, flammable degradation products (formaldehyde, methanol, and formic acid), and oxygen- or nitrous oxide-rich gases within the absorber provide all the ingredients necessary for combustion.¹⁹⁶ Avoiding the use of sevoflurane with strong base-rich absorbents (e.g., the now discontinued Baralyme), especially when desiccated, is the best way to prevent such complications. Anhydrous LiOH may also generate high temperatures by reacting with moisture from expired gas, but formulations of LiOH monohydrate do not.

A consensus statement established by the Anesthesia Patient Safety Foundation provides recommendations to reduce the risk of volatile anesthetic degradation by desiccated CO₂ absorbents¹⁶⁴:

- Turn off all gas flow when the machine is not in use
- Change the absorbent regularly
- Change the absorbent if color change indicates exhaustion
- Change all absorbent (not just one canister in a two-canister system)
- Change the absorbent when uncertain about the state of hydration (e.g., if fresh gas flow is left on for an extensive or indeterminate period of time)
- If compact canisters are used, change them more frequently

Given the improvements in absorbent chemistry detailed above, it seems prudent to select an absorbent that minimizes risk of adverse reactions whenever possible. Finally,

educating anesthesia personnel about these hazards and preventive measures may also reduce the likelihood of adverse events.

Indicators. Conventional absorbents contain an indicator dye, *ethyl violet*, that allows anesthesia personnel to visually assess the functional integrity of the absorbent. Ethyl violet is a substituted triphenylmethane dye that undergoes a color change around pH 10.3.¹⁶⁸ When the absorbent is fresh, the pH exceeds 10.3 and the dye is colorless. As the absorbent becomes exhausted, the pH drops below 10.3 and the dye becomes purple. The color change indicates that the absorptive capacity of the material has been depleted. Unfortunately, ethyl violet may not always be a reliable indicator. For example, prolonged exposure of ethyl violet to fluorescent light can photodeactivate the dye. When this occurs, the absorbent will remain white even when exhausted.¹⁹⁷ Similarly, color reversion (purple back to white) can occur with some absorbents due to the strongly alkaline nature of NaOH. Many newer indicators are resistant to color reversion, and several now endorse permanent color change. At least one absorbent contains no indicator and relies upon the detection of inspired CO₂ by the gas analyzer and/or a time schedule to trigger replacement.

Absorbent desiccation is impossible to detect by visual inspection. Therefore some newer generation Ca(OH)₂ absorbents also include desiccation indicators. Users should refer to the product manufacturer's literature to determine whether their absorbent uses this type of indicator.

Carbon Dioxide Removal Capacity and Absorber Resistance. The ability of the workstation's absorber to remove CO₂ is related to three main factors: (1) the amount of absorbent surface area exposed to the exhaled gas, (2) the intrinsic capacity of the absorbent to remove CO₂, and (3) the amount of nonexhausted absorbent remaining. The size and shape of the absorptive granules are intended to maximize surface area while minimizing resistance to airflow.¹⁹⁸ The smaller the granule size, the greater the surface area that is available for absorption. However, as particle size decreases, airflow resistance increases. The size and shape of the granules is proprietary, but most absorbents have a granule size between 4 and 8 mesh—a size at which surface area and resistance are optimized. (Mesh size refers to the number of openings per linear inch in a sieve through which the granular particles can pass. For example, a 4-mesh screen means that there are four quarter-inch openings per linear inch.¹⁶⁷) The presence of excess liquid water within the canister can decrease the exposed granule surface area and therefore the efficiency of CO₂ absorption.

As the absorbent granules stack up in canisters, small passageways inevitably form. These passages allow gas to flow preferentially through low-resistance areas. This phenomenon, known as *channeling*, may substantially decrease the functional absorptive capacity.¹⁹⁹ Recently, a nongranular polymer matrix product was released that binds particles together in a solid sheet of absorbent that has molded airflow channels, eliminating the phenomenon of channeling (personal communication, Micropore, Inc., Elkton, MD, June 3, 2014).

If completely reacted, a pound of Ca(OH)₂ has the capacity to absorb 0.59 lb of CO₂. LiOH has a higher capacity of 0.91 lb of CO₂ per pound.^{199a} Consequently, LiOH absorbents typically neutralize or "scrub" more CO₂ per unit weight (which is of great importance when planning submarine missions or space travel).^{199a,199b}

Mapleson Breathing Systems

In 1954, Mapleson described and analyzed five different breathing circuits, designated A through E (Fig. 22.40).²⁰⁰ In 1975, Willis and coauthors described the F system, which was added to the original five.²⁰¹ The Mapleson systems share certain features with the circle breathing system: they accept fresh gas flow, supply the patient with gas from a reservoir to meet inspiratory flow and volume requirements, and eliminate CO₂. They differ from the circle system by having bidirectional gas flow and lacking an absorber. To eliminate CO₂ and prevent rebreathing, these systems depend on a higher rate of fresh gas inflow. The Mapleson systems consist of several common components, including a connection point to a facemask or endotracheal tube, reservoir tubing, fresh gas inflow tubing, and an expiratory pop-off valve or port. All the circuits except for Mapleson E use a bag as an additional reservoir. The Mapleson A, B, and C systems are rarely used today, but the D, E, and F systems are commonly used. In the United States, the most popular representatives from the DEF group are the Bain circuit and the Jackson-Rees circuit.

Three distinct functional groups can be seen: A, BC, and DEF groups. The Mapleson A, also known as the "Magill circuit," has a spring-loaded pop-off valve located near the facemask. It is the only Mapleson circuit where fresh gas flow enters from the end of the circuit opposite the patient (in this case, near the reservoir bag). The Mapleson A is functionally quite different from the other circuits, and has drastically different performance when used for spontaneous versus controlled ventilation (see later). In the B and C systems, both the pop-off valve and fresh gas inlet tubing are located near the patient. The Mapleson C is known as the "Waters to-and-fro" circuit and lacks a corrugated tube. The reservoir tubing and breathing bag serve as a blind limb where fresh gas, dead space gas, and alveolar gas can collect. Finally, in the Mapleson D, E, and F, or "T-piece" group, fresh gas enters near the patient, and excess gas is vented off at the opposite end of the circuit. The Mapleson F circuit is known as the "Jackson-Rees" modification of the Mapleson E (also known as "Ayre's T-piece").

Even though the components and their arrangement are simple, functional analysis of the Mapleson systems is complex.^{202,203} The amount of CO₂ rebreathing with each system is multifactorial and affected by: (1) the fresh gas inflow rate, (2) minute ventilation, (3) ventilation mode (spontaneous or controlled), (4) tidal volume, (5) respiratory rate, (6) the inspiratory-to-expiratory ratio, (7) the duration of the expiratory pause, (8) peak inspiratory flow rate, (9) the volume of reservoir tubing, (10) the volume of the breathing bag, (11) the airway device being used (mask or endotracheal tube), and (12) the CO₂ sampling site.

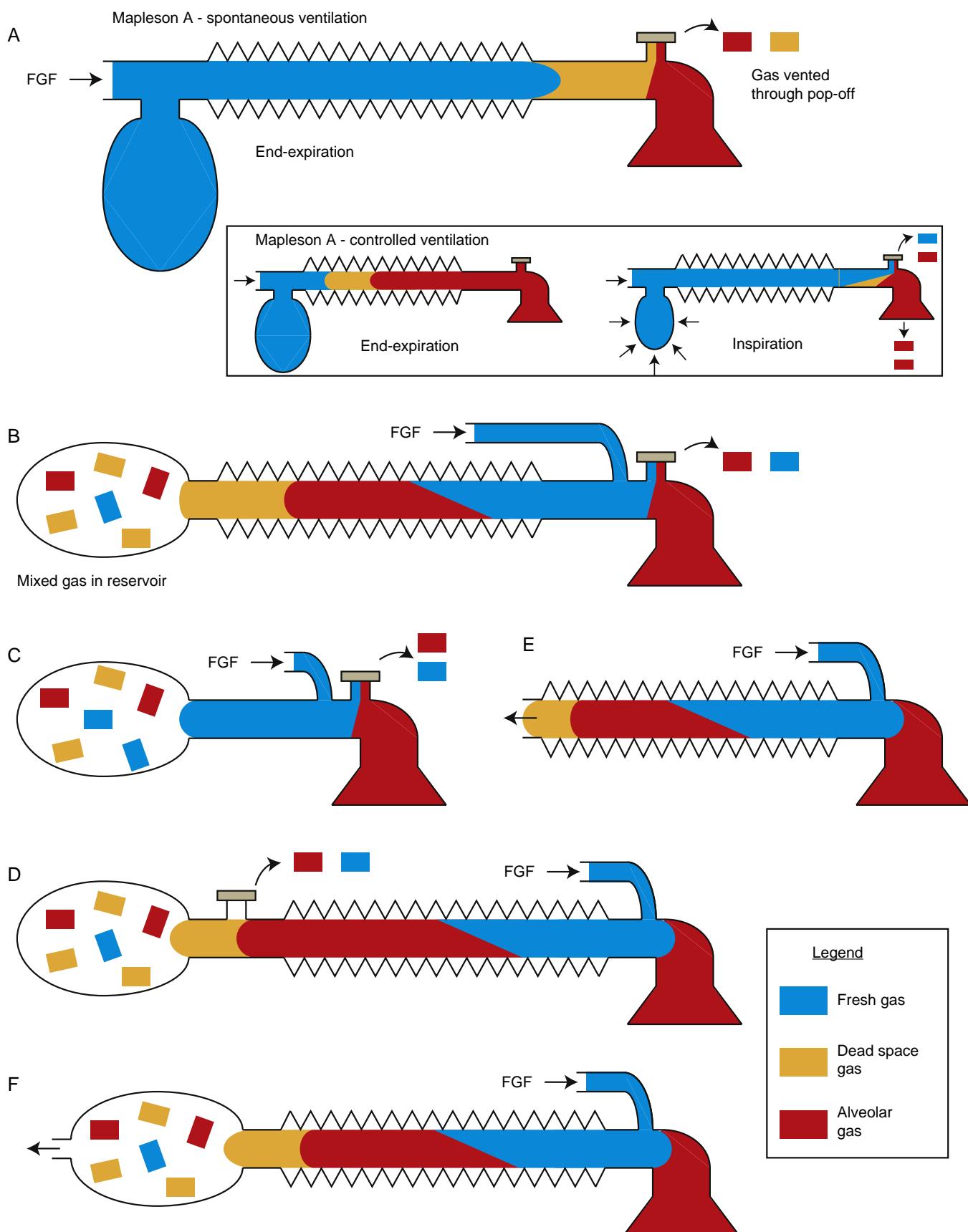


Fig. 22.40 Mapleson breathing systems. (A) Mapleson A system during spontaneous ventilation with gas distribution at end-expiration. A, Inset, Mapleson A system during controlled ventilation. (B–F) Mapleson systems B through F with gas distribution at end-expiration. FGF, Fresh gas flow. (Redrawn after Sykes MK. Rebreathing circuits. *Br J Anaesth.* 1968;40[9]:666–674; and Kaul TK, Mittal G. Mapleson's breathing systems. *Ind J Anaesth.* 2013;57[5]:507–519.)

Analysis of Gas Flow in the Mapleson A System. The performance of the Mapleson systems is best understood by studying the expiratory phase of the respiratory cycle.²⁰⁴ Illustrations of the gas distribution at end-expiration is shown for each system (see Fig. 22.40).^{204,204a} Of all the circuits, only the Mapleson A has markedly different performance when used for spontaneous versus controlled ventilation. During spontaneous ventilation, exhaled alveolar gas is vented through the pop-off during the expiratory phase (Fig. 22.40A). With the next inspiration, the patient primarily draws in fresh gas (and a small amount of dead space gas). Thus the Mapleson A has the best efficiency of the six systems for spontaneous breathing. A fresh gas inflow rate of greater than or equal to minute ventilation is sufficient to prevent rebreathing of CO_2 .²⁰⁵

However, the Mapleson A has the worst efficiency during controlled ventilation. As the reservoir bag is squeezed to initiate inspiration, exhaled alveolar gas first flows into the patient (Fig. 22.40A, inset). The pop-off valve then opens and vents significant amounts of the fresh gas stream away from the patient during the inspiratory phase.^{204a,205a} Significant rebreathing of CO_2 occurs unless minute ventilation is very high (>20 L/min). The key factor determining Mapleson A performance is the timing when the pop-off valve opens: during expiration for spontaneous ventilation, and during inspiration for controlled ventilation.²⁰⁶ Due to the location of the fresh gas inflow near the patient, the gas flow patterns of the other Mapleson systems (Fig. 22.40B–F) do not differ as markedly between spontaneous and controlled ventilation as that of the Mapleson A.

Relative Efficiencies. The “T-piece” systems DEF are slightly more efficient than systems BC. To prevent rebreathing CO_2 , the DEF systems require a fresh gas inflow rate of approximately 2 to 2.5 times minute ventilation, whereas the fresh gas inflow rates required for BC systems are somewhat higher.²⁰³ The reason for this improved efficiency is the location of the pop-off valve relative to the fresh gas inflow. With the BC systems, significant fresh gas is vented through the pop-off at end-expiration (Fig. 22.40B and C). With the DEF systems, fresh gas flow drives exhaled alveolar gas away from the patient to minimize rebreathing (Fig.

22.40E and F).^{204,205} The relative efficiency of different Mapleson systems with respect to prevention of rebreathing are: A > DFE > CB during spontaneous ventilation, and DFE > BC > A during controlled ventilation.^{200,203}

Advantages and Disadvantages. Mapleson systems have low resistance to gas flow, they are small and contain few parts, and changes in the fresh gas flow composition result in rapid changes in the breathing circuit. In addition, the volatile anesthetic agents within a Mapleson breathing circuit have no chance of degradation because of the absence of a CO_2 absorber. However, given their need for higher gas flows to prevent rebreathing, they are not as economical with regards to carrier gas and volatile anesthetic usage as the circle system. Conservation of heat and humidity is less efficient. Finally, scavenging of waste gas can be challenging, with the exception of the Mapleson D, which has the pressure-limiting valve located away from the patient.²⁰⁵

Bain Circuit

The Bain circuit is a coaxial circuit and a modification of the Mapleson D system (Fig. 22.41). Fresh gas flows through a narrow inner tube nested within the outer corrugated hose.²⁰⁷ The central fresh gas tubing enters the corrugated hose near the reservoir bag, but the fresh gas actually empties into the circuit at the patient's end. Exhaled gases pass down the corrugated hose, around the central tubing, and are vented through the pop-off valve near the reservoir bag.²⁰⁵ Exhaled gases passing down the outer corrugated hose add warmth to the inspired fresh gases by countercurrent heat exchange.

The main hazards related to use of the Bain circuit are an unrecognized disconnection or kinking of the inner fresh gas hose. These problems can cause hypercapnia as a result of inadequate gas flow or increased respiratory resistance. The outer corrugated tube should be transparent to allow ongoing inspection of the inner tube. The integrity of the inner tube can be assessed by sending high-flow oxygen into the circuit while the patient's end is occluded until the reservoir bag is filled.²⁰⁸ The patient's end is then opened, while oxygen is flushed into the circuit. If the inner tube is intact, the Venturi effect at the patient's end causes a decrease in

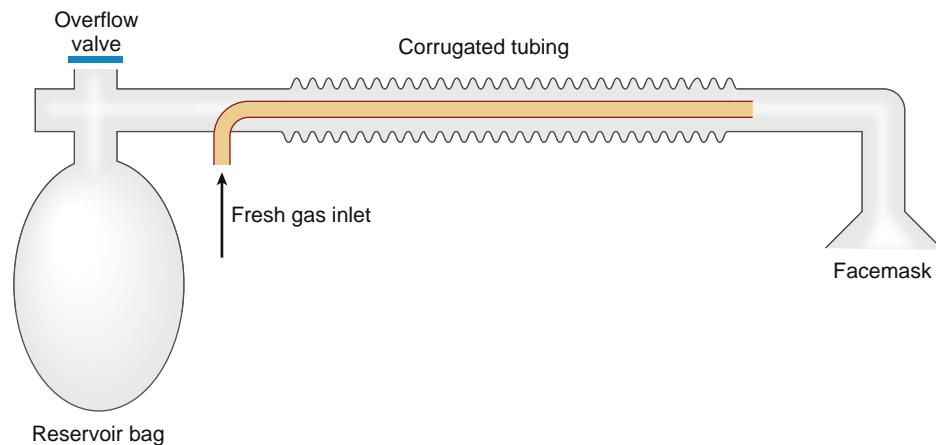


Fig. 22.41 The Bain circuit. (Redrawn from Bain JA, Spoerel WE. A streamlined anaesthetic system. *Can Anaesth Soc J*. 1972;19:426.)

pressure within the circuit, and the reservoir bag deflates. A leak in the inner tube allows fresh gas to escape into the expiratory limb, and the reservoir bag remains inflated. This test is recommended as part of the preanesthesia check if a Bain circuit is used.

Jackson-Rees Circuit. The Mapleson F circuit, also known as the “Jackson-Rees modification of the T-piece,” has function similar to the Mapleson D. It incorporates a hole in the end of the reservoir bag distal to the patient for venting of gases (Fig. 22.40F). The hole may be occluded by the operator’s hand to control bag distension and pressure, or fitted with a pop-off or PEEP valve for more precise control. The Jackson-Rees circuit is convenient for patient transport and preoxygenation during ICU or out-of-the-operating room procedures. The reservoir bag allows for easy tactile and visual monitoring of the patient’s respiratory effort. This circuit may be used for spontaneous (with the venting hole open), or assisted/controlled ventilation (with the venting hole partially or totally occluded). The Jackson-Rees is effective when connected to a face mask, endotracheal tube, laryngeal mask airway, or tracheostomy tube.

Like the Bain circuit, the Jackson-Rees has many advantages. It is lightweight, convenient, and potentially reusable (if sterilized). Being a Mapleson system, it has low resistance work of breathing. Fresh gas flows required to prevent rebreathing are approximately 2.5 to 3 times minute volume for spontaneous breathing, and 1.5 to 2 times minute volume for controlled ventilation.^{204a} Scavenging of gases from the expiratory valve is possible because the hole or valve is located away from the patient. Caution is advised when using HME filters between these Mapleson circuits and an endotracheal tube. Filters increase resistance and direct fresh gas flow away from the patient. An obstructed antimicrobial filter may produce hypoventilation and hypoxemia and mimic the signs and symptoms of severe bronchospasm.²⁰⁹

Self-Inflating Manual Resuscitators

While rarely used for delivery of inhaled anesthetics in modern practice, the manual resuscitation bag (e.g., Ambu bag, Laerdal resuscitator, or simply bag-valve-mask device) is an essential part of every anesthesia workstation. The key feature of this device is a compressible reservoir, typically made of silicone, that automatically expands upon release. Unlike the Mapleson circuits, the self-inflating manual resuscitator may be used for hand ventilation in the absence of an oxygen or air source. These devices are ubiquitous for patient transport, cardiopulmonary resuscitation, and for emergency back-up should the anesthesia machine ventilator or oxygen supply fail (see section on Checking Your Anesthesia Workstation).

In addition to the self-inflating reservoir bag, the manual resuscitator has several key components.^{134b} (1) A T-shaped *nonrebreathing valve* is located between the bag and the patient in order to direct gas flow throughout the respiratory cycle. During inspiration, the valve opens to allow flow from the reservoir bag to the patient, and the expiratory port is blocked (see Fig. 22.42). During exhalation, the inspiratory port (to the bag) is blocked, and the expiratory port opens to vent alveolar gas to atmosphere.

A variety of valve types exist (e.g., spring-disc, fishmouth). (2) An *inlet valve* permits refilling of the bag with reservoir gas or room air. (3) A *pop-off valve* may be present to limit the PIP, which can easily reach high levels with these devices.^{209a} ISO standards require that manual resuscitators designed for infants or children have a valve to limit PIP to 45 cm H₂O.^{209b} An override feature must be present should higher pressures be required (in case of poor lung compliance or high endotracheal tube resistance), and use of a manometer is recommended.

While manual resuscitators are extremely useful, portable, and convenient, they do have potential hazards.^{134b} Dangerously high inspiratory pressures may be generated if the operator is untrained, uncareful, or if valve failure occurs.^{209c} High pressures may lead to barotrauma or gastric insufflation. Similar to Mapleson circuits, significant variation of tidal volume, PIP, and PEEP is likely to occur when manual resuscitators are compared with mechanical ventilators.^{209d} Finally, the nonrebreathing valves generate resistance and may significantly increase the work of breathing during spontaneous ventilation.

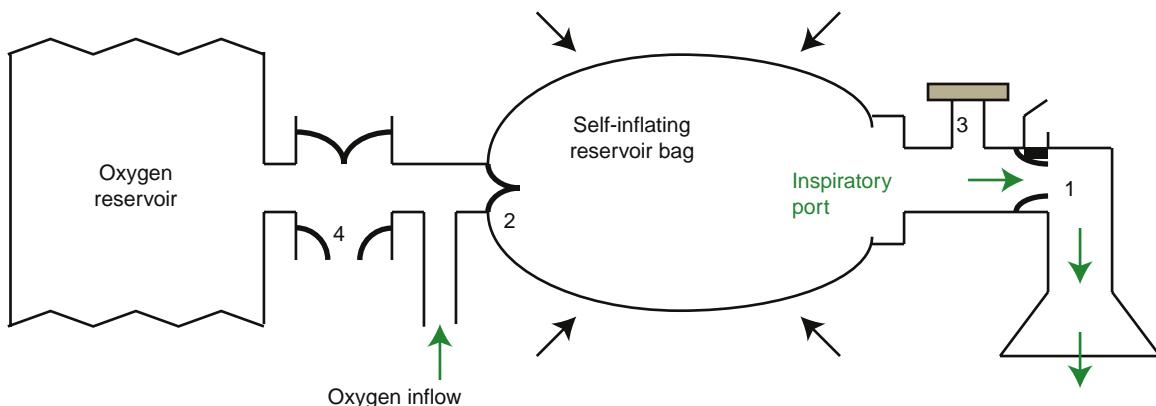
ANESTHESIA VENTILATORS

Automatic ventilation began to be added to anesthesia machines after the Second World War.^{209e} Historical draw-over systems relied only on spontaneous breathing by the patient. Later, breathing bags were added to anesthetic delivery devices to allow positive-pressure ventilation. Today’s anesthesia workstation ventilators incorporate ICU-like capabilities, including a variety of ventilation modes and the ability to allow for patient triggering. While ICU ventilators are simply open circuit, using entirely fresh gas for each breath, and venting all exhaled gas into the atmosphere, the anesthesia workstation must incorporate a means of collecting and redelivering the patient’s exhaled gas in the semi-closed circle system. This requirement presents unique engineering challenges in the design and control of the anesthesia ventilator. Historically the most common solution to this challenge has been the inclusion of a bellows in the anesthesia workstation. Alternative engineering solutions to allow rebreathing include piston-type ventilators, the Maquet volume reflector, or the Draeger Perseus’ turbine ventilator. The following discussion focuses on the classification, operating principles, and hazards associated with contemporary anesthesia ventilators.

Classification

Modern anesthesia ventilators can be best classified as either bellows or nonbellows. In bellows ventilators, the bellows serves as a volume reservoir for breathing gas, and the ventilator uses a double-circuit “bag in a bottle” design to deliver breaths. The bellows are typically driven pneumatically. Bellows-type ventilators can be subclassified as ascending or descending. The direction of bellows movement during the *expiratory phase* determines the bellows classification. An ascending (standing) bellows *ascends* during the expiratory phase, whereas a descending (hanging) bellows *descends* during the expiratory phase. Both types of bellows ventilators are illustrated in Fig. 22.43A and B. In nonbellows machines, the reservoir function may be served by the breathing bag itself (as in Draeger piston

A



B

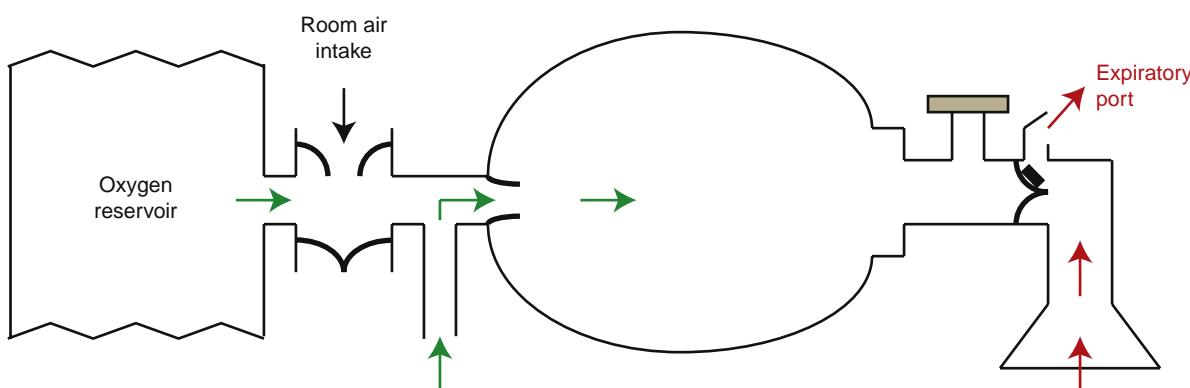


Fig. 22.42 Self-inflating manual resuscitator. (A) Flow of gas during inspiration. (1) Nonrebreathing valve, (2) bag inlet valve, (3) pop-off or pressure limiting valve (standard for pediatric and infant devices), and (4) outflow or excess-oxygen venting valve. (B) Flow of gas during expiration. See text for details. (Redrawn after Dorsch JA, Dorsch SE. The anesthesia machine. In Dorsch JA, Dorsch SE, eds. *Understanding Anesthesia Equipment*. 5th ed. Baltimore: Williams & Wilkins; 2008:83, Chapter 10 Manual Resuscitators; and Lien S, Verreault DJ, Alston TA. Sustained airway pressure after transient occlusion of a valve venting a self-inflating manual resuscitator. *J Clin Anesth*. 2013;25[5]:424–425.)

[see Fig. 22.43C] or turbine ventilators) or by the “volume reflector,” in the Maquet Flow-i anesthesia workstation. The drive mechanism of piston and turbine ventilators is mechanical, while the Maquet ventilator is pneumatically driven.

Additional classifications involve the modes of ventilation that are available. Older anesthesia machine ventilators operated only in a time-cycled manner, or as “controller ventilators,” without the ability to respond to a patient’s spontaneous breathing efforts. Modern machines that offer synchronized intermittent mandatory ventilation (SIMV), assist/control (A/C), and pressure support ventilation (PSV) must offer the ability for the patient to trigger breaths, and are referred to as “controller/noncontroller” ventilators. In contemporary anesthesia workstations, the responsiveness to patient triggering efforts is comparable to ICU ventilators, but the clinician should be on the lookout for evidence of asynchrony in modes that allow triggering.^{209f,209g} Contemporary anesthesia ventilators can function in volume-controlled or pressure-controlled modes. Finally, even though some ventilators may be pneumatically driven, all modern ventilators are under electronic control. The design of different anesthesia ventilators, with an emphasis on the integration between the ventilator and the circle breathing system, using specific workstations as examples are discussed below.

Pneumatically Driven Bellows Ventilator

The operating principle of the bellows ventilator is that it functions in a rigid airtight housing and serves as a reservoir for the patient’s breathing gas. The driving force used to move gas from the bellows back to the patient is pressurized gas that flows into the bellows’ housing under electropneumatic control. The bellows fills with the patient’s exhalation and fresh gas flow. Once the bellows is refilled, excess circuit gas is vented to the scavenging system during the expiratory pause. The mechanisms that vent breathing circuit waste gas during mechanical ventilation with bellows ventilators differ among manufacturers and models. The bellows ventilator is traditionally designated as a *double circuit*, meaning that the ventilator drive gas and the breathing gas exist in two separate circuits. The bellows serves as the interface between the breathing gas and the drive gas, much like the reservoir bag serves as the interface between the breathing gas and the anesthesia care provider’s hands.^{209h} Figs. 22.44 and 22.45 illustrate the inspiratory and expiratory phases of mechanical ventilation with an ascending bellows ventilator on the GE Aisys workstation. Note that the bellows ventilator uses pressurized gas from the intermediate-pressure section of the anesthesia machine to drive the bellows. On older bellows ventilators,

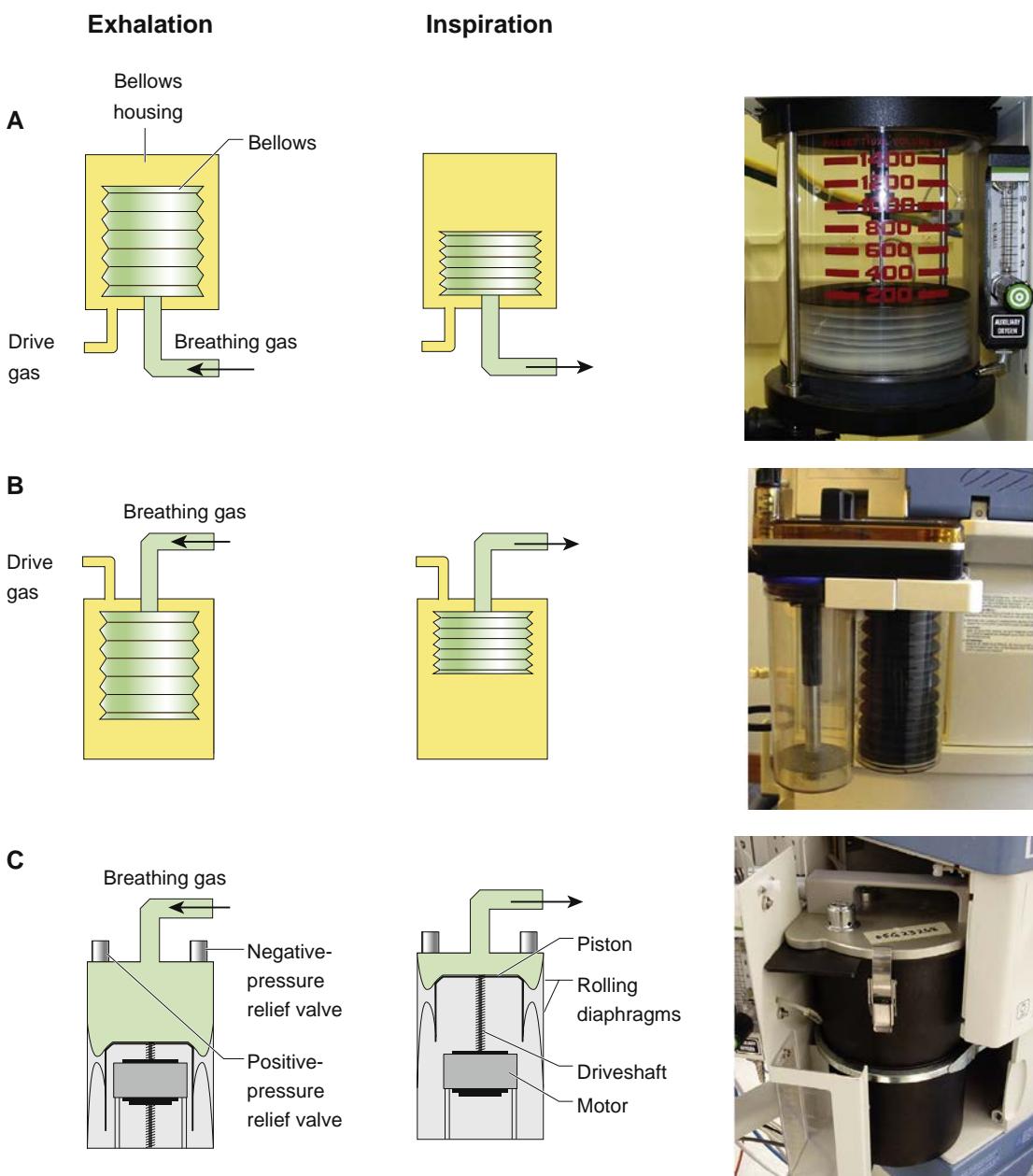


Fig. 22.43 Three types of anesthesia ventilators during exhalation (left) and inhalation (middle), with photo (right). To allow rebreathing and conservation of anesthetic gases, the anesthesia workstation ventilator must have a reservoir for the patient's exhaled breathing gas, just as the breathing bag does in manual and spontaneous modes of ventilation. This is a unique requirement of ventilators in anesthesia workstations. Intensive care unit ventilators, conversely, can simply vent exhaled gases into the environment. In the diagrams, breathing gas is green and ventilator drive gas is yellow. (A) Ascending bellows. (B) Descending (hanging) bellows. (C) Piston ventilator. See text for additional details. (Piston ventilator diagram modified from Yoder M. Ventilators. In: *Understanding Modern Anesthesia Systems*. Telford, PA: Dräger Medical; 2009.)

the user selected a tidal volume by setting a physical stop that restricted the bellows' filling (return stroke) to that point, making it a volume control ventilator.^{131a} The modern bellows ventilator has primary control over the pressure applied to the bellows, and uses data integrated from the flow sensors to create volume control breaths.

The source of the drive gas for the bellows is either oxygen or air, which is obtained from the gas supply section of the workstation. Some workstations allow for the selection of either oxygen or air as the ventilator drive gas, and some can entrain room air through a Venturi effect into the oxygen drive gas flow, thereby decreasing the oxygen

gas requirement. Knowing the type of gas used to drive the bellows ventilator can be important in oxygen failure emergencies. If oxygen is used as the drive gas, then the amount of oxygen consumed by the anesthesia machine will equal the amount of oxygen selected for fresh gas flow *plus* an amount approximately equal to the minute ventilation being delivered by the ventilator. Whereas a full E-cylinder can provide 10 hours of use with oxygen fresh gas flow of 1 L/min and manual ventilation through the circle system, that same E-cylinder will provide less than 2 hours' supply in an adult patient when oxygen is used as the ventilator drive gas.

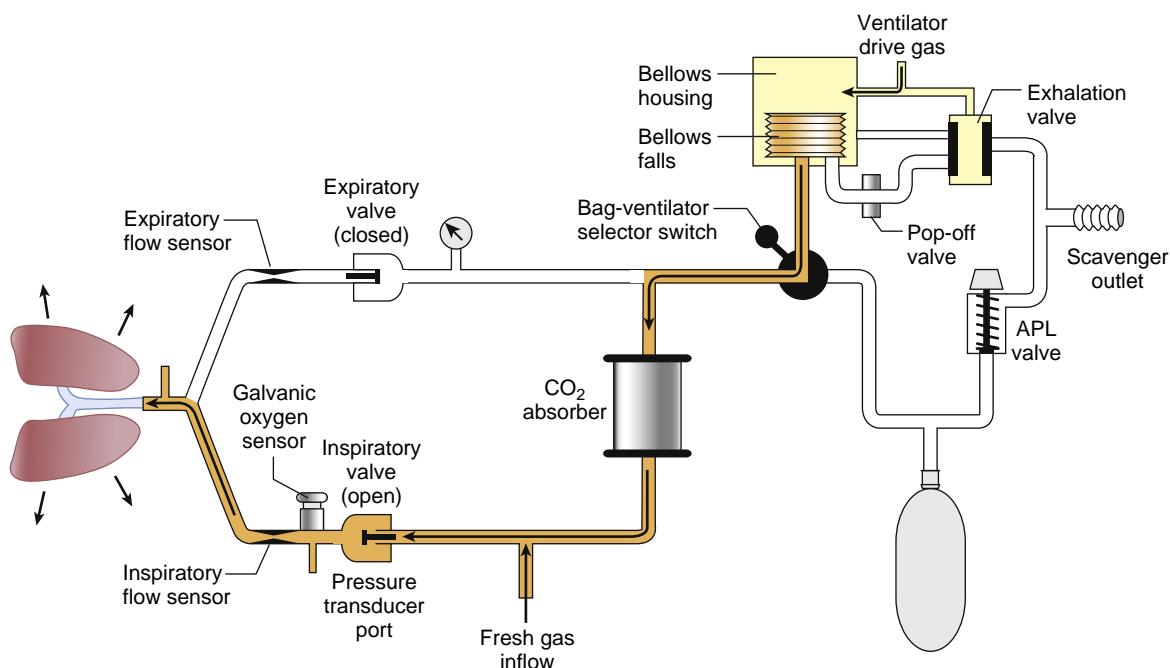


Fig. 22.44 **Inspiratory phases of ventilation with an ascending bellows ventilator represented by GE Aisys anesthesia workstation.** The ventilator drive gas circuit is located outside the bellows, and the patient's breathing circuit is inside the bellows. During the inspiratory phase the electronically controlled ventilator driving gas enters the bellows chamber and causes the pressure to increase, thereby compressing the bellows, which delivers gas to the patient's lungs. The drive gas also closes the exhalation valve and prevents the breathing gas from escaping into the scavenging system. Compensation for the impact of fresh gas flow on tidal volume accuracy is accomplished by monitoring the inhaled tidal volumes and adjusting ventilator drive gas volumes accordingly. *APL*, Adjustable pressure-limiting; *CO₂*, carbon dioxide. (Image courtesy Dr. Michael A. Olympio; modified with his permission. Adapted from Datex-Ohmeda. *Aisys Anesthesia Machine: Technical Reference*. Madison, WI: Datex-Ohmeda; 2005.)

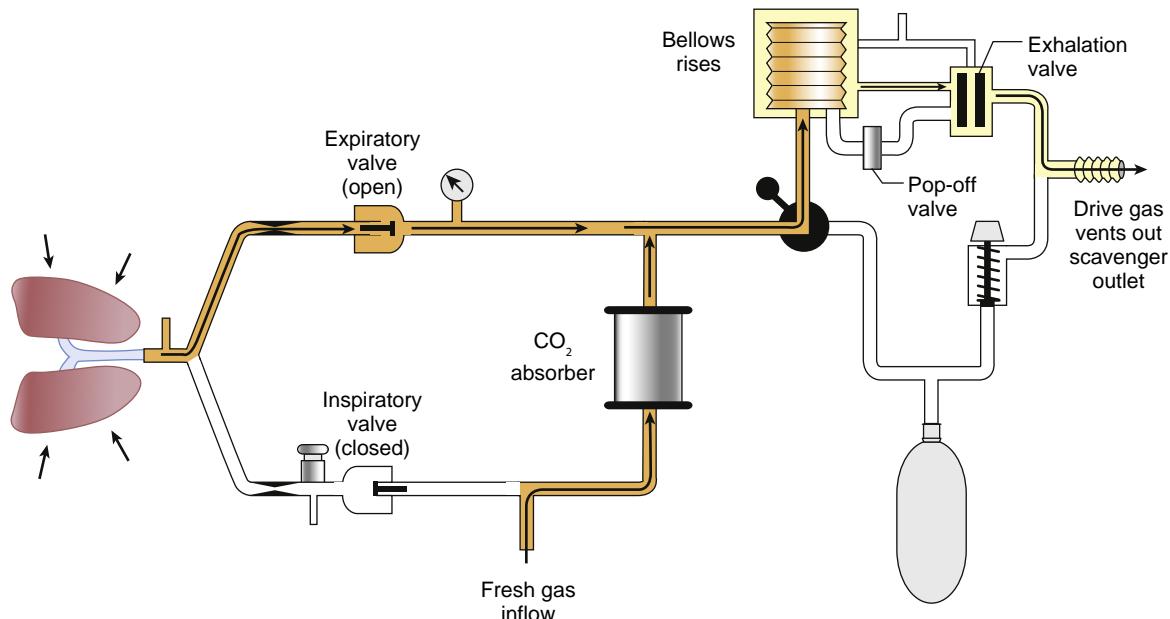


Fig. 22.45 During the early expiratory phase, the patient is able to exhale into the bellows because the ventilator exhalation valve is now open, thus allowing the drive gas in the bellows housing to vent through the scavenger outlet. The pop-off or ventilator relief valve prevents bellows gas from escaping at this point so the bellows can fill. In the late expiratory phase, positive end-expiratory pressure (PEEP) is provided by pressurization of the bellows housing and pressure modulation of the expiratory valve. (Courtesy Dr. Michael A. Olympio; modified with his permission. Adapted with permission from Datex-Ohmeda. *Aisys Anesthesia Machine: Technical Reference*. Madison, WI: Datex-Ohmeda; 2005.)

As described earlier, bellows-type ventilators can be classified according to the direction that they move during patient exhalation. Ascending bellows rise with exhalation, and descending bellows fall with exhalation (see Fig. 22.43). Older pneumatic ventilators and some newer anesthesia workstations use weighted descending bellows, but most contemporary bellows ventilators employ an ascending bellows design. Of the two configurations, the ascending bellows is considered safer. An ascending bellows will not fill if total disconnection occurs, or it may only partially fill if a circuit leak exceeds the fresh gas flow rate, providing an important visual cue for a circuit disconnect or leak. The bellows of a descending bellows ventilator, on the other hand, will continue its regular upward and downward movement despite patient disconnection: the drive gas pushes the bellows upward during the inspiratory phase, and during the expiratory phase the bellows “fills” with entrained room air instead of the patient’s exhaled gas, because of the weighted bellows. The pressure monitor and the volume monitor may be fooled even if disconnection is complete.³⁶ An essential safety feature of any anesthesia workstation that uses a descending bellows is an integrated CO₂ apnea alarm that cannot be disabled while the ventilator is in use.

Problems With Bellows Ventilators. Correct function of the bellows ventilator requires that both the bellows housing and the bellows itself be free of leaks. Improper seating of the plastic bellows housing can result in inadequate ventilation because a portion of the driving gas is vented to the atmosphere.²⁰⁹ A hole in the bellows can lead to alveolar hyperinflation and possibly barotrauma in some ventilators because high-pressure driving gas can enter the patient’s circuit. The oxygen concentration of the patient’s gas may increase when the driving gas is 100% oxygen, or it may decrease if the driving gas is composed of air or an air-oxygen mixture.²¹⁰

The ventilator relief valve (sometimes called the “exhalation valve”; see Fig. 22.44) can potentially cause problems. The function of this valve is to open during exhalation once the bellows has refilled, venting excess gas to the scavenger outlet. Hypoventilation can occur if the valve becomes incompetent because anesthetic gas is delivered to the scavenging system instead of to the patient during the inspiratory phase. Ventilator relief valve incompetency can result from a disconnected pilot line, a ruptured valve, or a damaged flapper valve.^{211,212} A ventilator relief valve stuck in the closed or partially closed position can cause either barotrauma or undesired PEEP.²¹³ Excessive suction from the scavenging system can draw the ventilator relief valve to its seat and close the valve during both the inspiratory and expiratory phases.³⁷ In this case, breathing circuit pressure escalates because the excess anesthetic gas cannot be vented. A number of manufacturers’ bellows-style anesthesia workstations send the used ventilator drive gas to the anesthesia gas scavenging system during exhalation. Under certain conditions, notably high fresh gas flows combined with high minute ventilation, the scavenging system can be overwhelmed, causing inadvertent high PEEP levels and/or pollution of the operating room with waste anesthetic gases (see section on scavenging systems). Other mechanical problems that can occur include leaks within the system, faulty pressure regulators, and faulty valves.

Mechanically Driven Piston Ventilator

Mechanically driven, electronically controlled piston-type ventilators use a computer-controlled stepper motor instead of compressed drive gas to deliver tidal volume (see Fig. 22.43). These are *single-circuit* ventilators, because there is not a separate ventilator drive gas circuit. The piston operates much like the plunger of a syringe in a cylinder of essentially zero compliance.^{131a} The ventilator has primary control over the volume displaced in the circuit and uses the data from pressure sensors to create pressure control breaths. The computerized controls can support a variety of ventilator modes, including pressure or volume limited breaths, in controlled, synchronized, or spontaneous modes.

Because the patient’s mechanical breath is delivered without the use of compressed gas to actuate a bellows, these systems consume dramatically less compressed gas during ventilator operation than do traditional pneumatic ventilators. This improvement in efficiency may have clinical significance when the anesthesia workstation is used in a setting where no pipeline gas supply is available (e.g., remote locations or office-based anesthesia practices). Another advantage of the piston ventilator is the potential for very accurate tidal volume delivery, because of the low compliance of the piston chamber. This is in contrast to bellows-type ventilators, in which the drive gas can be subject to varying degrees of compression. With either piston or bellows ventilators, feedback mechanisms that help maintain stable tidal volume delivery include circuit compliance compensation and the use of inspired tidal volume measurement as a feedback signal.

Figs. 22.46 and 22.47 illustrate the inspiratory and expiratory phases of mechanical ventilation with a piston ventilator, the Dräger Fabius workstation. Note the location of the ventilator within the breathing circuit between the fresh gas inflow and the inspiratory valve. The breathing bag participates in the circuit during mechanical ventilation, acting as the reservoir for rebreathing. The circuit employs a *fresh gas decoupling valve* to exclude fresh gas from being added to the tidal volume during inspiration. Therefore during inspiration the fresh gas is added to the breathing bag. During the expiratory phase, the breathing bag initially fills with exhaled gas; then, as the piston returns to its starting position, the fresh gas decoupling valve opens, and fresh gas flow plus gas from the breathing bag refill the piston chamber.

The piston in a piston ventilator tends to be fully or partially concealed from view, unlike the bellows on a bellows ventilator. The piston ventilator therefore does not naturally provide the visual feedback of a circuit disconnect or leak that is provided by the ascending bellows. However, the breathing bag, which serves as the reservoir during mechanical ventilation, moves with patient ventilation and can visually alert the provider to disconnect.

Additional feedback mechanisms have been incorporated on particular machines. For example, the Dräger Fabius Tiro has a transparent piston housing so that the user can visualize the motion of the piston, and the Dräger Apollo can be programmed to emit a breathing sound with the movement of the piston to provide an auditory cue.

A potential hazard associated with piston ventilators is that, like descending bellows ventilators, they will refill

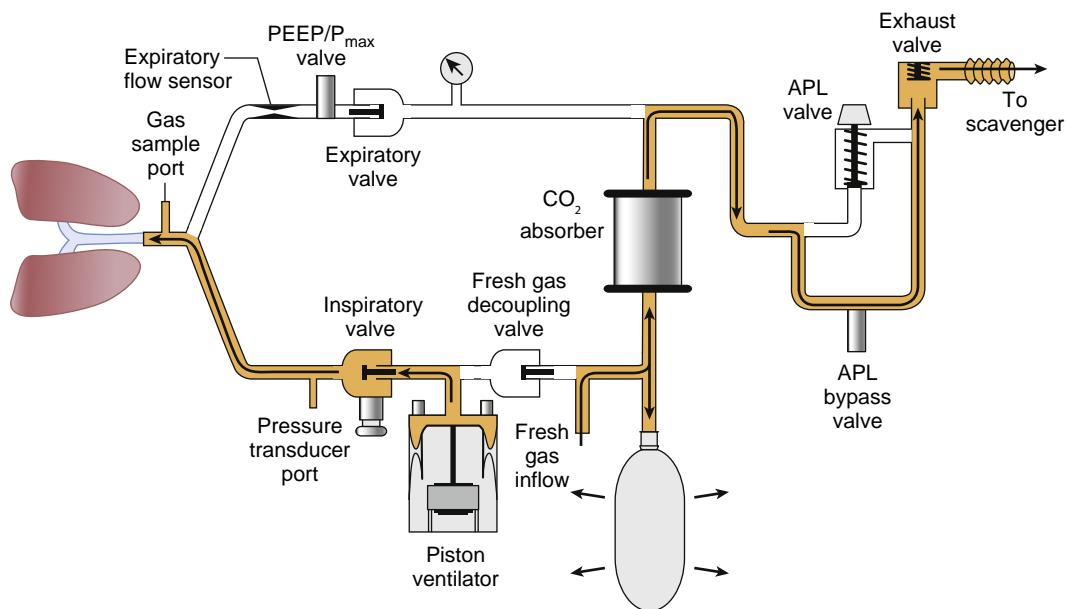


Fig. 22.46 **Inspiratory phase of ventilation with a piston ventilator represented by Dräger Fabius anesthesia workstation.** During inspiration, the positive end-expiratory pressure (PEEP)/maximum pressure (P_{max}) valve is held closed. The pressure in the breathing circuit that is generated by the ventilator closes the fresh gas decoupling valve. This directs fresh gas flow toward the breathing bag during inspiration so it does not interfere with tidal volume accuracy. Excess fresh gas flows past the open adjustable pressure-limiting (APL) bypass valve, through the exhaust check valve, and to the scavenger. Note how the breathing bag is integral to circuit function during mechanical ventilation. In the manual and spontaneous modes of ventilation, the piston ventilator is held in the upward position, and the APL bypass valve closes, thus making the APL valve operable. (Courtesy Dr. Michael A. Olympio; modified with his permission. Adapted from Dräger Medical. *Dräger Technical Service Manual: Fabius GS Anesthesia System*. Telford, PA: Rev: E, Dräger Medical; 2002.)

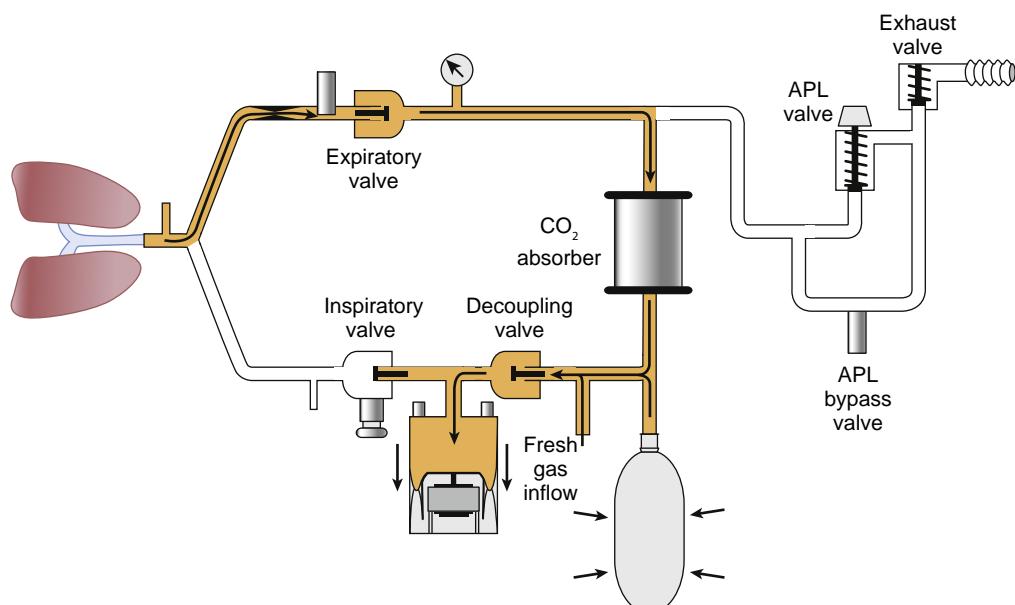


Fig. 22.47 During the initial phase of exhalation, before the piston begins moving back to starting position and the decoupling valve opens, the patient exhales into the breathing bag, and fresh gas continues to flow retrograde (not pictured). Once the decoupling valve opens, the piston's movement back to its starting position draws in gas stored within the breathing bag and fresh gas from the fresh gas inflow. Positive end-expiratory pressure (PEEP) is maintained by the PEEP/maximum pressure valve, which also prevents the ventilator from pulling in gas from the lungs. Once the piston reaches the bottom of its stroke, fresh gas flow reverses course and flows in retrograde fashion toward the breathing bag and the absorber (as in Fig. 22.46). Excess gas vents through the exhaust valve to the scavenger (Fig. 22.46). APL, Adjustable pressure-limiting. (Courtesy Dr. Michael A. Olympio; modified with his permission. Adapted from Dräger Medical. *Dräger Technical Service Manual: Fabius GS Anesthesia System*. Telford, PA: Rev: E, Dräger Medical; 2002.)

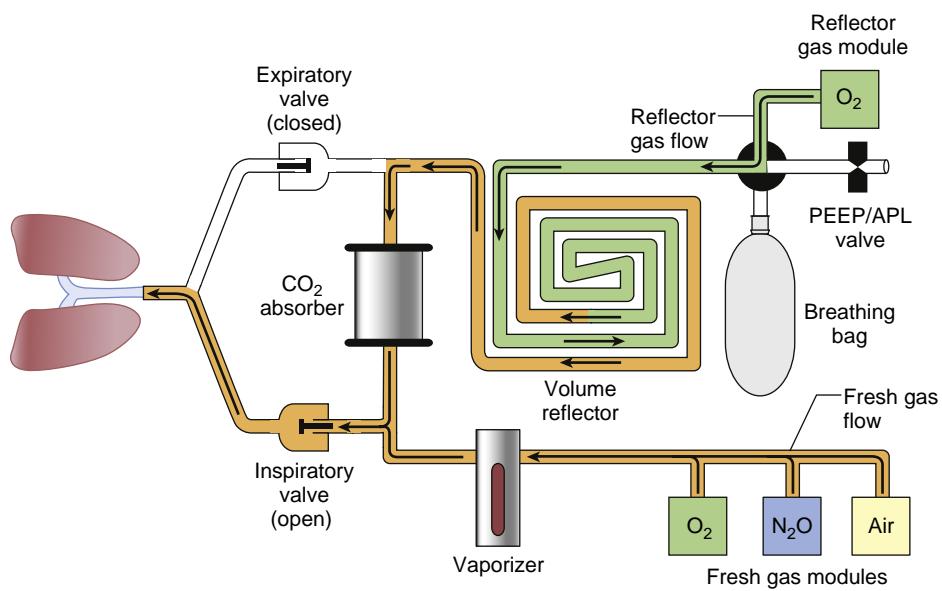


Fig. 22.48 Simplified schematic of the Maquet FLOW-i anesthesia workstation breathing circuit and gas supply system during inspiration in a controlled ventilation mode. The reflector gas module provides the driving force for ventilation by pushing gas out of the volume reflector to the patient. Volume reflector gas combines with the fresh gas flow downstream from the carbon dioxide (CO_2) absorber. APL, Adjustable pressure-limiting; N_2O , nitrous oxide; O_2 , oxygen; PEEP, positive end-expiratory pressure. See text for additional details. (Adapted from Maquet Critical Care. User's Manual: FLOW-i 1.2 Anesthesia System. Solna, Sweden: Rev: 11, Maquet Critical Care; 2011.)

even if a circuit disconnection occurs. Similarly, if a circuit leak is present, piston ventilators may entrain room air through the leak, thereby diluting oxygen and anesthetic agent. The associated risks are hypoxemia and awareness. The Dräger Fabius series piston ventilator will entrain room air through an auxiliary air valve, seen in Fig. 22.43, to fill the piston chamber if the fresh gas flow fails or is inadequate (instead of causing negative pressure in the breathing circuit). However, if this occurs, an alarm will alert the operator. A positive-pressure relief valve on the ventilator prevents excessively high breathing circuit pressure (60-80 cm H_2O).^{131a}

Maquet FLOW-i Anesthesia System With Volume Reflector

The Maquet FLOW-i anesthesia workstation uses a novel device called the *volume reflector* (Figs. 22.48 and 22.49) to act as the reservoir. The volume reflector is essentially a long plastic tube with a volume of 1.2 L, coiled compactly to fit in the anesthesia workstation. The volume reflector is functional and “in-circuit” during all modes of ventilation. It is interposed between the patient and the reflector gas module during positive-pressure ventilation or between the patient and the breathing bag during spontaneous or assisted ventilation. The volume reflector therefore acts as a volume reservoir while at the same time preventing mixing between the gas at the two ends of the tube.

Mechanical ventilation is powered by the *reflector gas module*, a solenoid-controlled oxygen flow source, which pushes gas out of the volume reflector through the CO_2 absorber and to the patient during inspiration, much like a piston (see Fig. 22.48). To understand the function of the volume reflector and reflector gas module, it is convenient to start with the expiratory phase (see Fig. 22.49), where exhaled patient gas fills the volume reflector’s proximal end (nearest the patient),

displacing reflector gas module gas out the PEEP valve and into the scavenging system. At the end of exhalation, the volume reflector is filled at the patient end with exhaled gas and is filled distally with a mixture of exhaled gases and reflector gas. The coiled design of the volume reflector prevents significant mixing between these gases of different compositions. The inspired tidal volume is generated by a combination of gas from the fresh gas modules and the reflector gas module, which work together in a coordinated manner to control gas flow and pressure in the breathing circuit so that operator-determined ventilation parameters are maintained. During mechanical ventilation on the FLOW-i, the fresh gas flow is not constant, but rather occurs primarily during inspiration. The inhaled anesthetic, if chosen, is injected into this flow (see earlier section on **Injection-Type Vaporizers**). All the gas modules use feedback loop-controlled, solenoid-actuated, pneumatic valves similar in function to those found in a servo-controlled ICU ventilator.²¹⁴

When the workstation is in the spontaneous mode of ventilation, the breathing bag is enabled, and the reflector gas module is disabled. The patient breathes in and out of the volume reflector, and circuit pressure is controlled by the operator-adjustable APL valve. Excess gases in controlled and spontaneous modes of ventilation are vented to the scavenger through the dual-function PEEP-APL valve.

The FLOW-i system can compensate for breathing system leaks by increasing reflector gas module flow. The operator is informed if this occurs. Because the reflector gas module provides only 100% oxygen, dilution of anesthetic gas occurs in this circumstance. The machine is nearly entirely electronically interfaced; therefore an emergency manual ventilation backup mode is provided for cases of system failure. This emergency backup mode provides an oxygen flow meter and mechanical APL valve linked to the patient circuit.²¹⁴

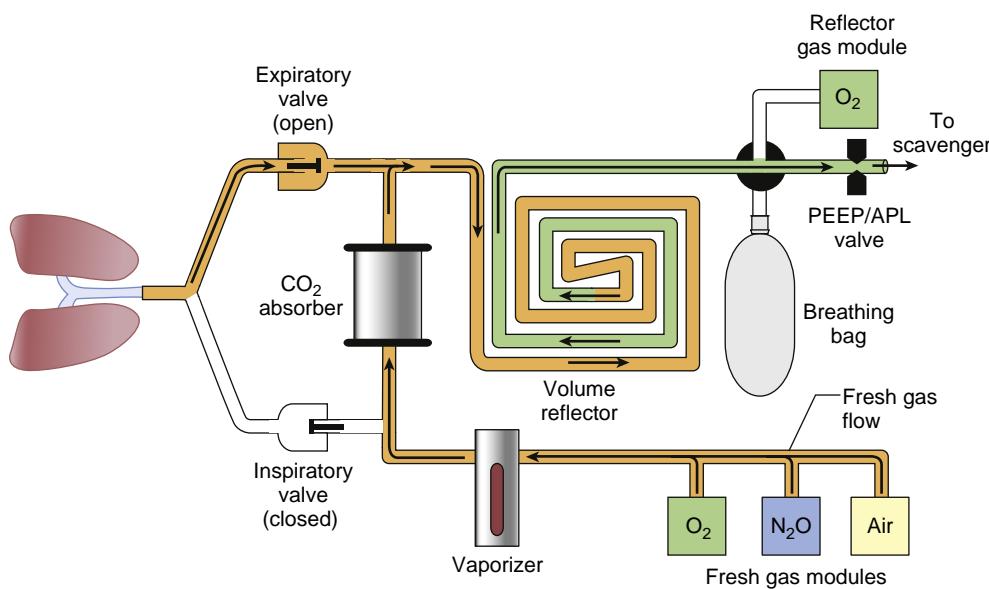


Fig. 22.49 Maquet FLOW-i breathing circuit and gas supply during exhalation in a controlled ventilation mode. The patient exhales into the volume reflector, which serves as an exhalation reservoir. The patient only partially fills the volume reflector. Fresh gas flows in retrograde fashion and combines with the exhaled gas. Excess gas is vented to the scavenger through the positive end-expiratory pressure (PEEP)/adjustable pressure-limiting (APL) valve, which also controls breathing circuit pressure (PEEP). When the machine is placed in the manual mode of ventilation, the breathing bag is enabled and the reflector gas module is disabled. In the manual mode, the patient breathes in and out of the volume reflector and can be assisted with the breathing bag. The PEEP/APL valve vents excess gas to the scavenger and controls breathing circuit pressure (continuous positive airway pressure). CO_2 , Carbon dioxide; N_2O , nitrous oxide; O_2 , oxygen. (Adapted from Maquet Critical Care. *User's Manual: FLOW-i 1.2 Anesthesia System*. Solna, Sweden: Rev. 11, Maquet Critical Care; 2011.)

Dräger Anesthesia Systems With Turbine Ventilators

A number of newer ventilators designed for the ICU utilize turbine technology to generate mechanical ventilation. Turbine ventilators use mechanical energy to spin a small turbine (fan) at very high speeds to create pressure and flow. Some possible functional advantages of turbine-based ventilators mentioned in bench testing include better responsiveness to patient triggering, more effective PSV, and, in some cases, more accurate tidal volume delivery under high ventilatory workload.^{214a,214b,214c}

The Dräger Zeus and Perseus workstations incorporate turbine-type ventilators (Figs. 22.50 and 22.51). In constructing an anesthesia workstation, the major advantage of the turbine is that it can be placed directly within the circle system. Unlike the bellows or volume reflector, it does not require a separate quantity of gas to move the patient's tidal volume; and unlike a piston, it does not require refilling. During inspiration (see Fig. 22.50), the turbine blower generates flow and pressure directed into the inspiratory limb of the patient circuit, drawing gas from the breathing bag, which serves as a reservoir during mechanical ventilation. The fresh gas flow is incorporated as part of this inspiratory flow. During exhalation (see Fig. 22.51), exhaled gas fills the bag before escaping to the scavenging system, and that portion of the fresh gas flow that occurs during exhalation travels in the reverse direction toward the bag as well. As in the piston ventilators, the breathing bag is an integral part of the circuit during mechanical ventilation, continuing to serve a reservoir function. Unlike the piston ventilators, the turbine ventilator design implies that the breathing bag empties during inspiration and refills during expiration. The bag's motion may serve as a visual

indicator of ventilation, and depending on set fresh gas flow, of circuit leak.

Unlike the piston, the turbine is primarily a pressure generator. The ventilator utilizes flow sensors and electronic controls to generate a number of modes of mechanical ventilation, including volume and pressure control, pressure support, and airway pressure release ventilation. In the spontaneous mode of ventilation, the operator may dial in a CPAP level.

Target-Controlled Inhalational Anesthesia

During traditional operation of the anesthetic workstation, the anesthesia provider controls the composition of the fresh gas flow that is added to the circle system every minute. Since this fresh gas mixes with the gases already in the circle breathing system, there may be a significant difference between the composition of the fresh gas flow and the final concentration of the inspired (or expired) gases. As the fresh gas flow is decreased, there may be a greater difference between the fresh gas composition and the actual inspired concentrations. If the oxygen in the fresh gas flow is less than the patient's metabolic oxygen requirement, then the amount of oxygen extracted from the circle breathing circuit every minute is more than the amount added, and the inspired gas will eventually become hypoxic.^{214d} Reducing the fresh gas flow reduces the total amount of anesthetic agent used, which reduces cost and the environmental footprint. However, low-flow anesthesia can be challenging in practice, as it is easier to control the patient's actual inspired gas composition when the fresh gas flow is high.

On anesthesia workstations where the flow control valves and the anesthetic vaporizers are under electronic

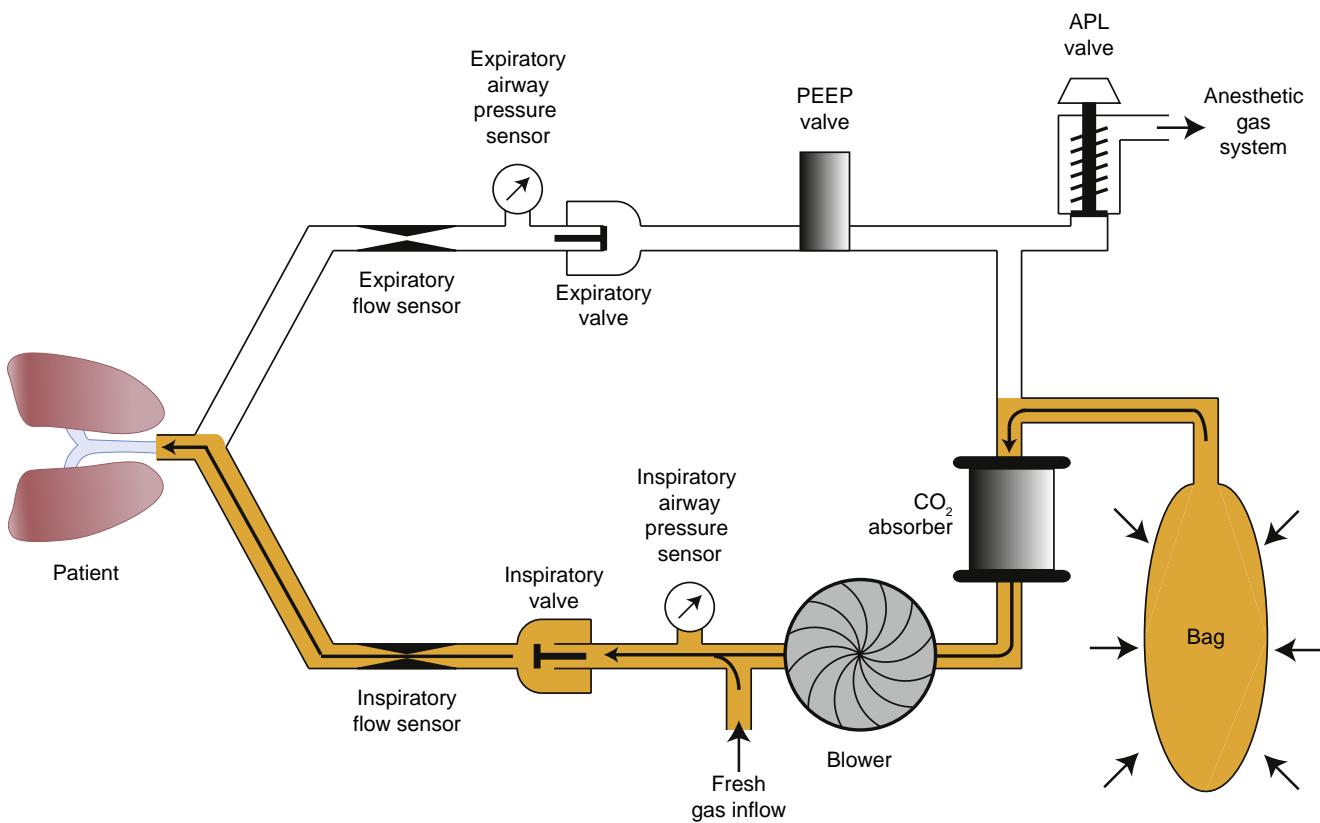


Fig. 22.50 Simplified schematic of the Dräger Perseus anesthesia workstation breathing circuit and gas supply system. During inspiration the positive end-expiratory pressure (PEEP) valve is held closed and pressure is generated by the turbine blower. There is no fresh gas decoupling valve. The flow generated by the blower draws gas from the breathing bag, which acts as a reservoir during mechanical ventilation, through the carbon dioxide (CO_2) absorber, and to the patient. In the manual and spontaneous modes of ventilation, the blower is passive, allowing the adjustable pressure-limiting (APL) valve to control the pressure in the breathing circuit. (Adapted from Drägerwerk AG & Co. Technical Documentation IPM: Perseus A500 and Perseus A500 Ceiling. Lübeck, Germany: Rev: 5.0; n.d.)

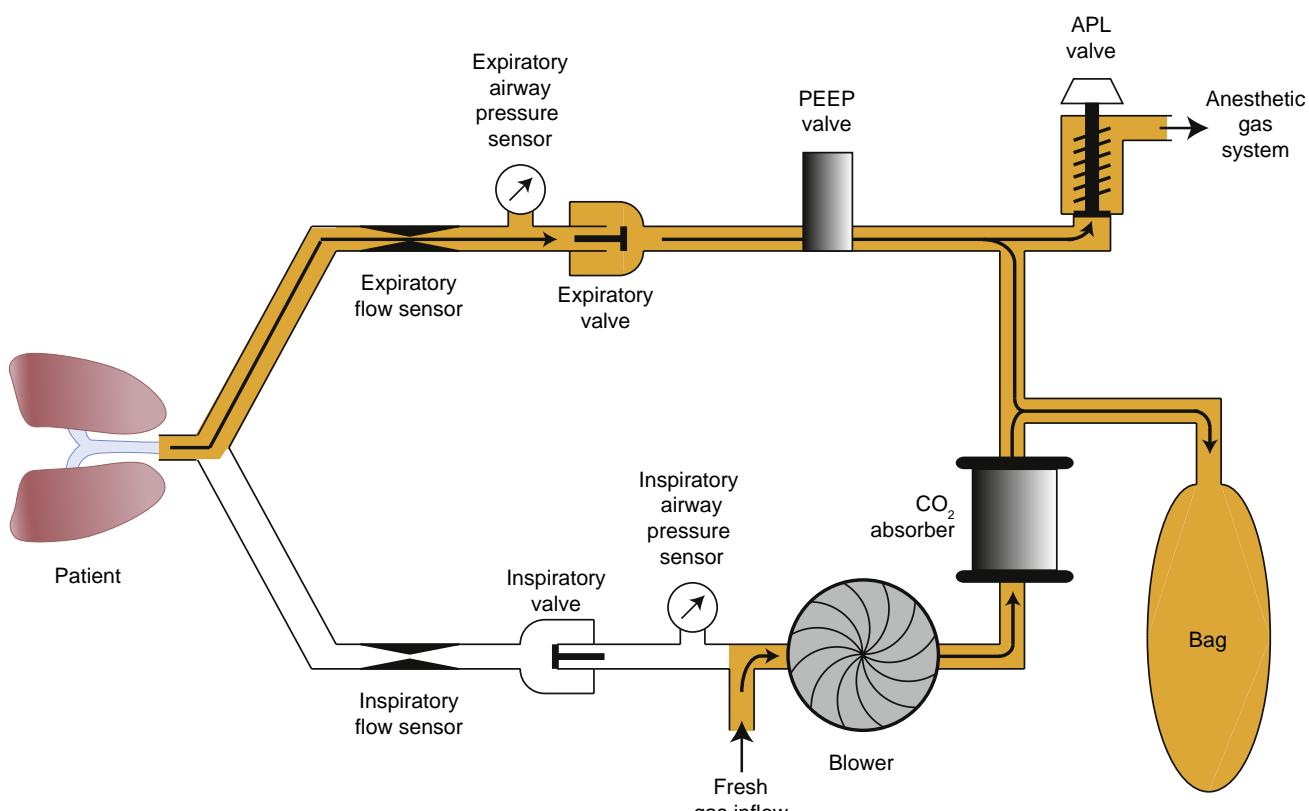


Fig. 22.51 Dräger Perseus anesthesia workstation breathing circuit and gas supply system during exhalation phase of controlled ventilation. The exhalation phase begins when the positive end-expiratory pressure (PEEP) valve opens and exhaled gas fills the breathing bag. The portion of fresh gas that flows during the exhalation phase also flows retrograde toward the breathing bag. Excess flow is vented to the anesthetic gas system (scavenging). Note that the adjustable pressure-limiting (APL) valve is not active during controlled ventilation. PEEP is maintained by a separate valve. CO_2 , Carbon dioxide. (Adapted from Drägerwerk AG & Co. Technical Documentation IPM: Perseus A500 and Perseus A500 Ceiling. Lübeck, Germany, n.d., Rev: 5.0.)

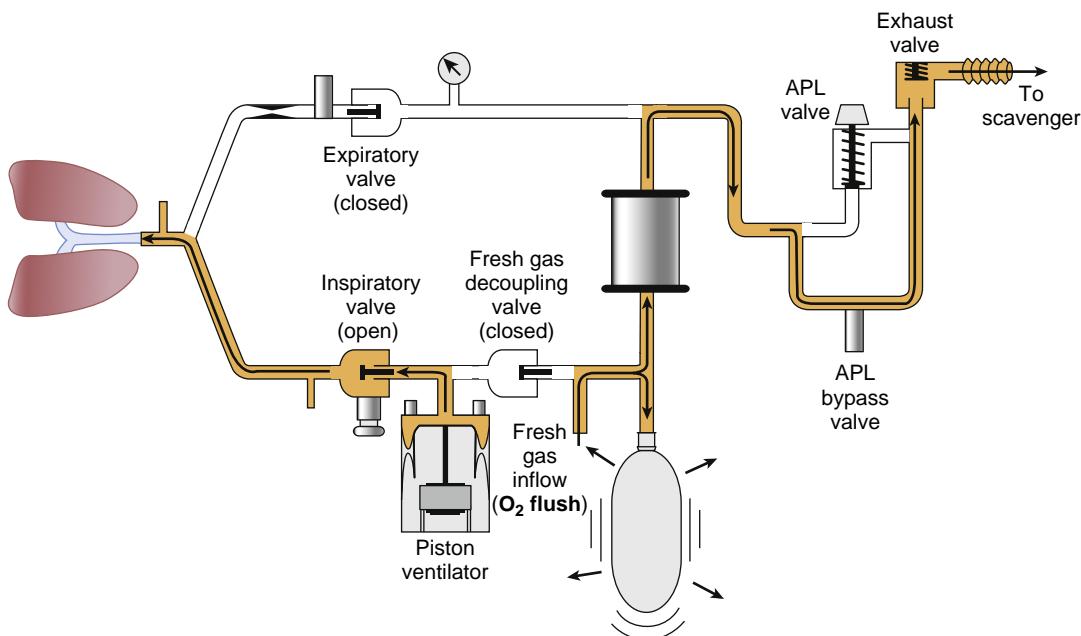


Fig. 22.52 Fresh gas decoupling during an oxygen (O_2) flush shown on the Dräger Fabius workstation. During inspiration the positive end-expiratory pressure/maximum pressure valve is held closed. The pressure in the breathing circuit that is generated by the ventilator closes the fresh gas decoupling valve. This directs the high-volume oxygen flush flow toward the breathing bag during inspiration so it does not contribute to inhaled tidal volume and breathing circuit pressure. The O_2 flush gas also flows past the open adjustable pressure-limiting (APL) bypass valve, through the exhaust check valve, and to the scavenger. (Modified image courtesy of Dr. Michael A. Olympio. Adapted from Dräger Medical: *Dräger Technical Service Manual: Fabius GS Anesthesia System*. Rev. E. Telford, PA: Dräger Medical; 2002.)

control, it is possible to implement *target-controlled inhalational anesthesia*. The targets subject to control are the end-tidal anesthetic agent and the end-tidal oxygen concentration. Currently, Dräger, GE, and Maquet all have target-controlled systems available. The major advantage of the target control is reduced consumption of anesthetic agent.^{214f-214h} These systems rely on proprietary algorithms, and the actual savings may depend on how fast the algorithm tries to achieve the desired anesthetic depth. The target-controlled system might actually prioritize rapid achievement of set anesthetic agent (requiring high initial fresh gas flow) over reducing fresh gas flow and anesthetic agent consumption.²¹⁴ⁱ The benefits of low-flow anesthesia could be realized by a vigilant anesthesia provider, but at the expense of significantly more key-strokes per case.^{214h} Although the target-controlled modes of inhalational anesthesia seem likely to reduce anesthetic agent use, and to provide an additional layer of patient safety in low-flow anesthesia, none are currently approved by the FDA for use in the United States.

Fresh Gas Flow Compensation and Fresh Gas Decoupling

On older bellows-type anesthesia workstations, the portion of fresh gas flow that occurred during an inspiratory cycle was added to the set tidal volume, leading to variation in tidal volume depending on the set fresh gas flow. During the inspiratory phase of mechanical ventilation, the ventilator relief valve (also known as the ventilator pop-off valve) is typically closed, and the breathing system's APL valve is most commonly out of circuit. Therefore during positive-pressure ventilation, the patient's lungs received the volume from the bellows in addition to that from the flowmeters

during the inspiratory phase. The amount of excess volume (and pressure) that the patient received was proportional to the direction and magnitude of the change in the fresh gas flow rate. As the practitioner turned up the fresh gas flow, the tidal volume increased. The opposite would occur if the flow rate were decreased from the baseline. It was therefore common knowledge that the operator needed to adjust the set tidal volume on the ventilator if the total fresh gas flow rate was changed to maintain stable tidal volumes and airway pressure.

Newer workstations have engineering features that provide compensation of fresh gas flow to maintain stable tidal volume delivery. Broadly speaking, the workstation will either exclude the fresh gas from the inspiratory limb of the circuit during inspiration, or it will use electronic controls to compensate for the fresh gas flow's contribution. The precise manner in which this is accomplished accounts for much of the variation in breathing system design. On the Dräger Fabius workstation, a principle called *fresh gas decoupling* is used to prevent changes in the fresh gas flow rate from altering positive-pressure tidal volumes and breathing circuit pressures. During the inspiratory phase of ventilation, a decoupling valve located upstream from the piston ventilator diverts the fresh gas stream toward the breathing bag and scavenge outlet during each positive-pressure breath (Fig. 22.52). The GE Aisys system, on the other hand, uses inspiratory tidal volume measurement as a feedback signal for the automatic adjustment of ventilator drive gas volume to compensate for changes in fresh gas flow and leaks.^{214j}

On workstations without a fresh gas decoupling feature, inappropriate activation of the oxygen flush valve during the inspiratory phase of mechanical ventilation can add a

substantial amount of volume to the circuit and can result in baro- and/or volutrauma because excess pressure and volume may not be able to be vented from the breathing circuit.²⁵ Although the circuit high-pressure alarm may provide warning, unless an adjustable inspiratory pressure limiter is set to a relatively low value, high pressures can be realized. On workstations equipped with adjustable inspiratory pressure limiters, maximal inspiratory pressure may be set by the user to a desired peak airway pressure. An adjustable pressure relief valve opens when the predetermined user-selected pressure is reached. This theoretically prevents the generation of excessive airway pressure. However, this feature depends on having preset the appropriate pop-off pressure. If the setting is too low, insufficient pressure for ventilation may be generated and can result in inadequate minute ventilation; if set too high, the excessive airway pressure may still occur and result in patient harm. Some machines may also include a factory-preset inspiratory pressure safety valve that opens at a preset airway pressure, such as 60 to 80 cm H₂O, to minimize the risk of barotrauma. Therefore modern workstations without fresh gas decoupling usually reach a maximum pressure limit and terminate ventilation, release pressure, or sustain at the pressure limit.²¹⁵ In machines with a fresh gas decoupling feature, the oxygen flush inflow is diverted away from the patient during positive-pressure ventilation, thereby maintaining stable volumes and pressures.

SCAVENGING SYSTEMS

Scavenging is the collection and subsequent removal of waste anesthetic gases from both the anesthesia machine and the anesthetizing location. Scavenging is required because the fresh gas flow rates used during most anesthetic regimens deliver more anesthetic agent than necessary, as well as more oxygen than is being consumed. Without scavenging, operating room personnel could be exposed to anesthetic gases, and there could be an increased risk of an oxygen-rich environment supporting combustion.

In 1977, the National Institute for Occupational Safety and Health (NIOSH) prepared a document entitled *Criteria for a Recommended Standard: Occupational Exposure to Waste Anesthetic Gases and Vapors*.²¹⁶ Although it was maintained that a minimal safe level of exposure could not be defined, the NIOSH proceeded to issue the recommendations shown in Table 22.9. These same criteria remain in place today. Contemporary scavenging systems are governed by standards set forth by the ISO.^{11,216a} In 1999, the ASA Task Force on Trace Anesthetic Gases developed a booklet entitled *Waste Anesthetic Gases: Information for Management in Anesthetizing Areas and the Postanesthesia Care Unit*. This publication describes the role of regulatory agencies, reviews scavenging and monitoring equipment, and provides recommendations.²¹⁷ Finally, the Occupational Safety and Health Administration (OSHA) publishes *Anesthetic Gases: Guidelines for Workplace Exposures* on its website; this document does not establish legal standards, but is a repository of information, guidelines, and references.^{217a}

The two major causes of waste gas contamination in the operating room are the anesthetic technique used and equipment issues.^{217,218} Regarding the anesthetic

TABLE 22.9 National Institute for Occupational Safety and Health Recommendations for Trace Anesthetic Gas Levels

Anesthetic Gas	Maximum TWA Concentration (ppm)*
Halogenated agent alone	2
Nitrous oxide	25
Combination of halogenated agent plus nitrous oxide	
Halogenated agent	0.5
Nitrous oxide	25
Dental facilities (nitrous oxide alone)	50

*Time-weighted average sampling, also known as time-integrated sampling, is a sampling method that evaluates the average concentration of anesthetic gas over a prolonged period, such as 1 to 8 hours.

TWA, Time-weighted average.

From U.S. Department of Health, Education and Welfare. *Criteria for a Recommended Standard: Occupational Exposure to Waste Anesthetic Gases and Vapors*. Washington, DC: U.S. Department of Health, Education and Welfare; 1977.

technique, causes of operating room contamination include: (1) failure to turn off the gas flow control valves or the vaporizer when the circuit is disconnected from the patient; (2) use of poorly fitting masks; (3) flushing of the circuit into the room; (4) filling of anesthetic vaporizers, particularly if spillage occurs; (5) use of uncuffed endotracheal tubes; and (6) use of breathing circuits other than the circle system. Equipment failure or lack of understanding of proper equipment use can also contribute to operating room contamination. Leaks can occur in the high-pressure hoses, the nitrous oxide tank mounting, the high- or low-pressure circuits of the anesthesia machine, or the circle system, particularly at the CO₂ absorber assembly. The anesthesia care provider must be certain that the room suction and scavenging system is operational and adjusted properly to ensure adequate scavenging. Waste flow from a side-stream gas analyzer (50-250 mL/min) must also be directed to the scavenging system or returned to the breathing system to prevent pollution of the operating room.^{217,218}

Classifications and Components

Waste anesthesia gas scavenging systems can be classified as: *active* or *passive*. In active systems, the scavenging system is connected to a vacuum source, such as the hospital's suction system. Passive systems simply vent the waste gas into a heating, ventilation, and air conditioning (HVAC) system or through a hose to the building's exterior through a wall, ceiling, or floor. Passive systems rely only on the slight positive pressure of the gases leaving the gas-collecting assembly to provide the flow. If the passive system vents to an HVAC system, it is mandatory that it be a *nonrecirculating* system. Passive systems are less common in contemporary operating rooms.

Scavenging systems may also be *open* or *closed*. An open scavenging system allows for room air to be entrained into the flow of waste gas, whereas a closed system does not.²¹⁹ This distinction is discussed more thoroughly below.

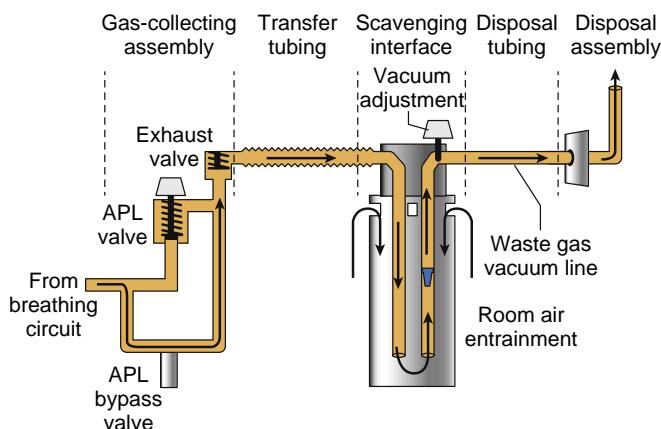


Fig. 22.53 Components of a scavenging system using the example of a Dräger Fabius system (Dräger Medical, Telford, PA) connected to an open, active scavenging system. The transfer tubing has a connector size distinct from the breathing circuit to prevent misconnections. Obstructions in the gas-collecting assembly or transfer tubing can cause high pressure in the breathing circuit. Leaks, inadequate suction, or failure of the scavenging interface can cause environmental contamination. APL, Adjustable pressure-limiting. See text for details. (From Brockwell RC. Delivery systems for inhaled anesthesia. In: Barash PG, ed. *Clinical Anesthesia*. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2006:589.)

Scavenging systems classically have five components (Fig. 22.53): (1) the gas-collecting assembly, (2) the transfer tubing, (3) the scavenging interface, (4) the gas disposal assembly tubing, and (5) an active or passive gas disposal assembly.²²⁰

Gas-Collecting Assembly. The gas-collecting assemblies are where waste gas exit from the breathing circuit and connect to the transfer tubing. Waste anesthetic gases are vented from the anesthesia system either through the APL valve or through some sort of ventilator relief valve. Excess patient exhaled gas must exit the breathing system through one of these valves or be shed into the room (e.g., poor face-mask fit, endotracheal tube leak, machine leak). Ventilator drive gas on contemporary bellows-type ventilators, as well as the flow from the reflector gas module on the Maquet FLOW-i, are vented via the scavenging system as well. This is significant because under conditions of high fresh gas flow and high minute ventilation, the gases flowing into the scavenging interface may overwhelm the evacuation system. If this occurs, waste anesthetic gases may overflow the system through the positive-pressure relief valve (closed systems) or through the atmospheric vents (open systems) and pollute the operating room. This scenario is less likely with pneumatically driven ventilators that exhaust their drive gas (100% oxygen or oxygen/air mixture) into the operating room through a small vent on the back of the ventilator control housing.

Transfer Tubing. The transfer tubing carries excess gas from the gas-collecting assembly to the scavenging interface. As specified by ISO standard 80601-2-13, the scavenging system must have 30-mm connectors, or some other proprietary connector that will prevent the scavenging system from connecting to other elements on the workstation.¹¹ Some manufacturers color-code the transfer tubing

with yellow bands to distinguish it from 22-mm breathing system tubing. The tubing must be sufficiently rigid to prevent kinking to minimize the chance of occlusion, or it must contain some means of pressure relief in case of occlusion. Occlusion of the transfer tubing can be very problematic because it is upstream from the pressure-limiting features of the scavenging interface. If the transfer tubing is occluded by kinking or misconnection, breathing circuit pressure will increase and barotrauma can occur.^{144,221-223} On machines that have separate transfer tubes for the APL valve and for the ventilator relief valve, the two tubes merge before or at the scavenging interface.

Scavenging Interface. The scavenging interface is the most important component of the system because it protects the breathing circuit or ventilator from excessive positive or negative pressure.²²⁰ The interface should limit the pressure immediately downstream from the gas-collecting assembly to between -0.5 and $+3.5$ cm H₂O under normal working conditions.¹¹ Positive-pressure relief is mandatory irrespective of the type of disposal system used, so the system can vent excess gas in case of occlusion (or inadequate suction with active systems) downstream from the interface. If the disposal system is an active system, negative-pressure relief will also be necessary to protect the breathing circuit or ventilator from excessive subatmospheric pressure. Subatmospheric pressure in the scavenging system could induce gas flow from the patient's breathing system. A reservoir is highly desirable with active systems because it stores waste gases until the evacuation system can remove them.

OPEN INTERFACES. The open scavenge interface sets up a continual flow into the disposal tubing using an active interface. If the amount of waste gas being discharged from the anesthesia workstation is less than the continual flow in the scavenging system, then the balance of that flow is obtained from entrained room air. Because the anesthesia machine discharges waste gas intermittently in surges, peak flow may overwhelm the flow of the scavenging system, so open systems also require a reservoir canister (Fig. 22.54).²¹⁹ Waste gas enters the system at the top of the canister and travels to the bottom through an inner tube, where a vacuum line removes waste gases. When adjusted properly, the vacuum rate should exceed the rate of waste gas flow into the chamber, and some room air should also be drawn into the canister through the relief port. The vacuum flow rate is usually adjusted on the scavenging interface using a flow control valve and flowmeter. Adjusting the scavenger vacuum flow rate is an important part of the workstation daily pre-use checkout procedure. If vacuum flow is inadequate, waste gas can spill out into the room through the relief ports. The open system does not require positive- or negative-pressure relief valves because the canister is open to the atmosphere. Relief ports on the top of the canister provide positive- and negative-pressure relief. Some open scavenging systems can incorporate a reservoir bag instead of a canister.

CLOSED INTERFACES. Closed scavenging interfaces are isolated from the environment by pressure relief valves, so the relationship of waste gas flow, vacuum flow, and the size of the system's reservoir bag determines the effectiveness of the gas elimination. All closed interfaces must have a positive-pressure relief valve to vent excess system pressure in

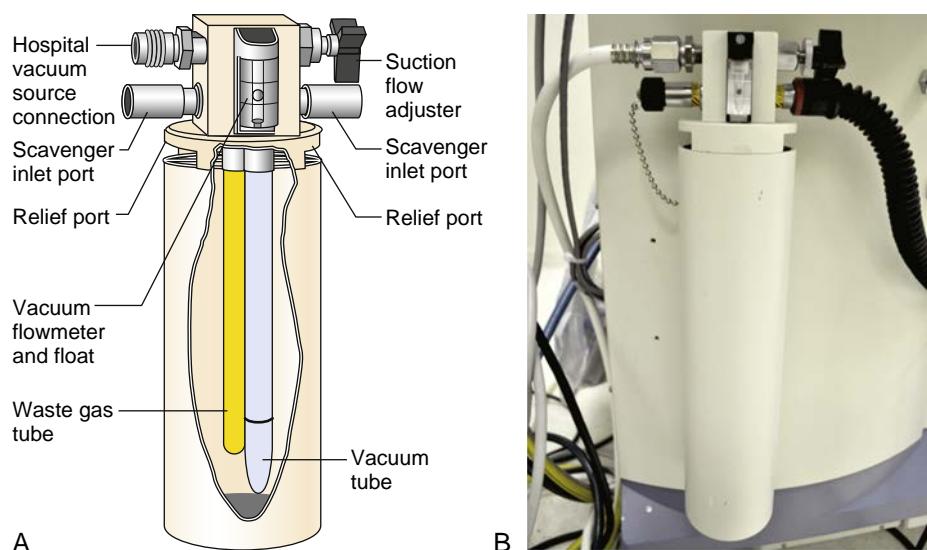


Fig. 22.54 (A and B) Open scavenging interface. When adjusted properly, room air is continually entrained via the relief port the top of the cannister. See text for details.

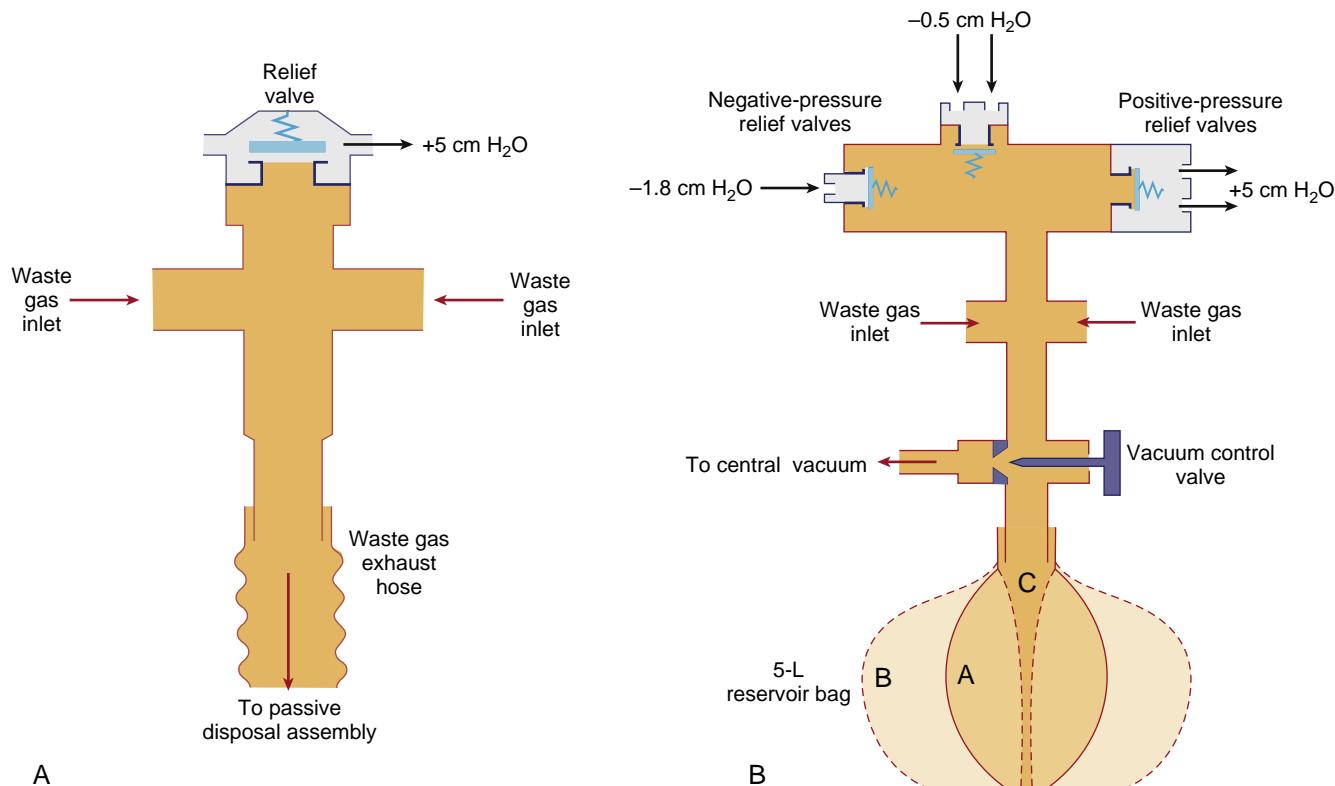


Fig. 22.55 Closed scavenging interfaces. (A) Interface used with a passive disposal system. (B) Interface used with an active system. In Panel B the labels on the 5-L reservoir bag refer to proper adjustment (A), over-distention (B), and completely deflated (C). See text for additional details. (A, Modified from North American Dräger. *Scavenger Interface for Air Conditioning: Instruction Manual*. Telford, PA: North American Dräger; 1984; B, From North American Dräger. *Narkomed 2A Anesthesia System: Technical Service Manual*. Telford, PA: North American Dräger; 1985.)

case of obstruction and a negative-pressure relief valve to protect the breathing system from subatmospheric pressure if an active disposal system is used.²²⁰

Two types of closed interfaces are used in clinical practice. One is used with passive scavenging systems and has positive-pressure relief only; the other is used with active scavenging systems and has both positive- and negative-pressure relief.

POSITIVE-PRESSURE RELIEF ONLY. A *closed, passive scavenging system* requires only a single positive-pressure relief valve (Fig. 22.55A). Waste gas enters the interface at the waste gas inlets. Transfer of the waste gas from the interface to the disposal system relies on the slight positive pressure of the gases leaving the patient's breathing system because a negative-pressure evacuation system is not used. Waste gases are then passively vented to a nonrecirculating HVAC

system or to the outdoors. The positive-pressure relief valve opens at a preset value (such as 5 cm H₂O) if an obstruction between the interface and the disposal system occurs.²²⁴ With this type of system, a reservoir bag is not required.

POSITIVE- AND NEGATIVE-PRESSURE RELIEF. A *closed, active* scavenging system requires a positive-pressure relief valve and at least one negative-pressure relief valve, in addition to a reservoir bag. Fig. 22.55B, is a schematic of Dräger Medical's closed scavenging interface for active suction systems. A variable volume of waste gas intermittently enters the interface through the waste gas inlets. The reservoir bag intermittently accumulates excess gas until the evacuation system eliminates it. The operator must adjust the vacuum control valve so that the reservoir bag remains properly inflated (see Fig. 22.55B, label A), and neither overdistended (label B) nor completely deflated (label C). Gas is vented to the operating room atmosphere through the positive-pressure relief valve if the system pressure exceeds a preset pressure (varies depending on manufacturer). Room air is entrained through the negative-pressure relief valve if the system pressure is more negative than that valve's opening pressure, approximately -0.5 cm H₂O. Some systems have a backup negative-pressure relief valve that opens at -1.8 cm H₂O if the primary negative-pressure relief valve becomes occluded by dust or other causes. The effectiveness of a closed system in preventing spillage depends on the rate of waste gas inflow, the evacuation flow rate, and the size of the reservoir. Leakage of waste gases into the atmosphere occurs only when the reservoir bag becomes fully inflated and the pressure increases sufficiently to open the positive-pressure relief valve. A "high PEEP" or sustained airway pressure alarm is often encountered in this circumstance.

Gas Disposal Assembly Conduit or Extract Flow. The gas disposal assembly conduit conducts waste gas from the scavenging interface to the receiving end of the gas disposal system (see Fig. 22.53). It should be collapse-proof and should run overhead, if possible, to minimize the chance of accidental occlusion. The connection to the scavenging interface can be a permanent or proprietary connector, but the connection to an active gas disposal system should be a DISS-type connector.²²⁵

Gas Disposal System. The gas disposal assembly ultimately eliminates excess waste gas (see Fig. 22.53). The two types of environmental disposal mechanisms, active and passive, have been described.

Hazards

Scavenging systems minimize operating room pollution, yet they add complexity to the anesthesia system. A scavenging system functionally extends the anesthesia circuit all the way from the anesthesia machine to the ultimate disposal site. This extension increases the potential for problems. Excessive vacuum applied to a scavenging system can cause undesirable negative pressures within the breathing system. Obstruction of scavenging pathways can cause excessive positive pressure in the breathing circuit. Even when the patient is protected from barotrauma by positive-pressure relief valves, alarm conditions can contribute to potentially unsafe conditions.²²⁶ Inadequate vacuum to the interface can cause venting of waste gas into the operating room. An unusual report linked fires in engineering equipment rooms

BOX 22.3 Requirements for Safe Delivery of Anesthesia Care

- Reliable delivery of oxygen at any appropriate concentration up to 100%.
- Reliable means of positive-pressure ventilation.
- Backup ventilation equipment available and functioning.
- Controlled release of positive pressure from the breathing circuit.
- Anesthesia vapor delivery (if intended as part of the anesthetic plan).
- Adequate suction.
- Means to conform to standards for patient monitoring.

From Sub-Committee of American Society of Anesthesiologists Committee on Equipment and Facilities: *Recommendations for Pre-Anesthesia Checkout Procedures* (2008).

to design of some waste gas scavenging systems in which the waste gases were vented into machine rooms that have vents opening to the outside as opposed to directly outside.^{21,230}

Checking Your Anesthesia Workstation

A complete preanesthesia checkout procedure (PAC) must be performed each day before the anesthesia workstation is first used, and an abbreviated version should be performed before each subsequent case. Box 22.3 lists seven basic requirements for safe delivery of anesthesia care drawn from the ASA's *Recommendations for Pre-Anesthesia Checkout Procedures*.^{11b} The anesthesia provider must have assurance prior to commencing any anesthetic that these requirements have been met. Institutions should develop and detail local procedures for meeting these basic safety requirements. These local procedures have taken on increased importance as increasing machine diversity make the applicability of a single, generic PAC remote.

Despite the fact that a PAC has been a mandatory part of anesthesia practice for over 30 years,²²⁸ evidence suggests that anesthesia providers frequently do not perform a complete PAC,^{6,229} and may miss faults even when explicitly looking for them on a sabotaged machine.³ Furthermore, all contemporary anesthesia workstations have automated checkout procedures, none of which can assure that all the basic safety requirements for delivery of anesthetic care have been met.^{8,231} In their 2008 *Recommendations*, the ASA suggests that many anesthesia providers are not fully aware of what elements are checked by the automated procedures.^{11b} Even review of user's manuals does not always make it obvious.

The ASA's *Recommendations for Pre-Anesthesia Checkout Procedures*, summarized in Box 22.4, focus on ensuring the *availability* of key equipment, and assessing the *function* of that equipment. The *Recommendations* also give guidance as to which items may be carried out by a technician (such as an anesthesia technician or biomedical technician). When the party responsible is listed as "provider and technician," then the provider must perform that task; the task may also be assigned to the technician as an added layer of safety. Each institution should develop their own procedures in which the specific duties are delineated.

BOX 22.4 Summary Recommendations of the 2008 Preanesthesia Checkout Procedures

Items to Be Completed Daily

Item #	Task	Responsible Parties?
1	Verify that auxiliary oxygen cylinder and self-inflating manual ventilation device are available and functioning	Provider and technician
2	Verify that patient suction is adequate to clear the airway	Provider and technician
3	Turn on the anesthesia delivery system and confirm that AC power is available	Provider or technician
4	Verify the availability of required monitors, including alarms	Provider or technician
5	Verify that pressure is adequate on the spare oxygen cylinder mounted on the anesthesia machine	Provider and technician
6	Verify that the piped gas pressures are ≥ 50 psig	Provider and technician
7	Verify that vaporizers are adequately filled and, if applicable, that the filler ports are tightly closed	Provider only
8	Verify that the gas supply lines have no leaks between the flowmeters and the common gas outlet	Provider or technician
9	Test the scavenging system function	Provider or technician
10	Calibrate, or verify the calibration of, the oxygen monitor, and check the low-oxygen alarm	Provider or technician
11	Verify that carbon dioxide absorbent is not exhausted	Provider or technician
12	Perform breathing system pressure and leak testing	Provider and technician
13	Verify that gas flows properly through the breathing circuit during both inspiration and exhalation	Provider and technician
14	Document the completion of checkout procedures	Provider and technician
15	Confirm the ventilator settings, and evaluate readiness to deliver anesthesia care (Anesthesia Time Out)	Provider only

Items to Be Completed Before Each Procedure

Item #	Task	Responsible Parties?
1	Verify that patient suction is adequate to clear the airway	Provider and technician
2	Verify the availability of required monitors, including alarms	Provider or technician
3	Verify that vaporizers are adequately filled and, if applicable, that the filler ports are tightly closed	Provider only
4	Verify that carbon dioxide absorbent is not exhausted	Provider or technician
5	Perform breathing system pressure and leak testing	Provider and technician
6	Verify that gas flows properly through the breathing circuit during both inspiration and exhalation	Provider and technician
7	Document the completion of checkout procedures	Provider and technician
8	Confirm the ventilator settings, and evaluate readiness to deliver anesthesia care (Anesthesia Time Out)	Provider only

Modified from Sub-Committee of American Society of Anesthesiologists Committee on Equipment and Facilities: *Recommendations for Pre-Anesthesia Checkout Procedures* (2008).

2008 RECOMMENDATIONS FOR PRE-ANESTHESIA CHECKOUT PROCEDURES

The items in [Box 22.4](#) are reviewed here. Fifteen items are required before commencing the day's anesthesia procedures. Eight items (see [Box 22.4](#), items 2, 4, 7, 11-15) are required before each case.

Item 1: Verify Auxiliary Oxygen Cylinder and Self-Inflating Manual Ventilation Device Are Available and Functioning

Frequency: Daily

Responsible parties: Provider and technician

The anesthesia provider must always be prepared to keep the patient alive without the assistance of the anesthesia machine. The most important safety check in any anesthesia location prior to commencing the day's procedures is the presence of a self-inflating manual ventilation device and a source of oxygen that is separate from the anesthesia workstation and hospital pipeline oxygen supply. These items must be present at every anesthetizing location. The *Recommendations* advise checking the function of the self-inflating ventilation device; this can typically be done

without opening the packaging. Note that the presence of a non-self-inflating Mapleson-type breathing circuit is *not* adequate to meet this item.

The auxiliary oxygen tank, typically an E-cylinder, should be checked to make sure it is full, and also for the presence of an attached flowmeter and a means to open the cylinder valve. After check, the valve should be closed to prevent inadvertent loss of the contents. Ensuring the presence of properly filled portable cylinders with attached flowmeters and cylinder wrenches benefits from the logistical support of support staff, but must ultimately be verified by the anesthesia provider.

Item 2: Verify Patient Suction Is Adequate to Clear the Airway

Frequency: Before each use

Responsible parties: Provider and technician

"Safe anesthetic care requires the immediate availability of suction to clear the airway if needed."^{11b} Adequate suction with tubing of appropriate length and an oral suctioning tool (e.g., Yankauer suction tip) are necessary before the start of any case. Since these are normally changed with every case, this item is often shared between provider and technician. The provider must verify this item prior to commencing the anesthetic.

Item 3: Turn on Anesthesia Delivery System and Confirm That AC Power Is Available

Frequency: Daily

Responsible party: Provider or technician

Contemporary anesthesia workstations have backup battery power if wall power should fail. If a case is inadvertently started on battery backup power, the first obvious sign of power failure can be catastrophic system shutdown when the backup batteries are exhausted. Prior to commencing the day's anesthetic procedures, functioning AC power should be verified. The ASA also recommends verifying power supply to component subsystems such as desflurane vaporizers. This item may be completed by technician or provider.

Item 4: Verify Availability of Required Monitors and Check Alarms

Frequency: Before each use

Responsible party: Provider or technician

The ASA *Recommendations* include in this item both the presence of monitoring supplies (blood pressure cuffs of appropriate sizes, pulse oximetry probes, etc.), functional tests of critical monitoring equipment (pulse oximeter and capnography), and functional tests of alarm conditions. The importance of an audible alarm is emphasized.

Some elements of this item are straightforward, such as verifying the availability of the monitoring equipment and making sure that monitors are on and cables are properly plugged in. However, the process of checking alarm thresholds, and possibly resetting them, can be tedious. Monitor alarm settings may possibly vary within individual facilities as a result of provider manipulation of alarms for case requirements, a lack of standard default settings, and failure to reset alarm limits routinely. Departmental alarm default settings can be established and programmed into anesthesia workstation monitors. Alarm limit settings also include anesthesia machine alarms such as volume, pressure, and inspired oxygen concentration limits. The practitioner should ensure that critical alarm limits are set to values that permit these alarms to do what they were intended to do. Here, anesthesia technicians can improve the quality of the pre-use checkout by checking the function of standard monitors and confirming that critical alarm thresholds are set to established default values.

Item 5: Verify That Pressure Is Adequate on the Spare Oxygen Cylinder Mounted on the Anesthesia Machine

Frequency: Daily

Responsible parties: Provider and technician

In addition to verifying the presence of a separate source of cylinder oxygen (Item 1), the anesthesia provider should verify the presence of an adequately filled oxygen cylinder mounted on the anesthesia workstation. Verification of oxygen cylinder pressure is accomplished by opening the oxygen cylinder or cylinders on the back of the machine and evaluating the tank gauge pressure. The current recommendations do not provide a specific value that would prompt replacing the tank, but some manufacturer's manuals suggest changing the oxygen cylinder when the pressure is below 1000 psi.^{31a}

The *Recommendations* affirm that other gas supply cylinders such as air, nitrous oxide, etc., need to be checked only if that gas is required for the anesthetic.

Item 6: Verify That Piped Gas Pressures Are 50 psig or Higher

Frequency: Daily

Responsible parties: Provider and technician

A daily check of adequate pipeline pressures is specified in the *Recommendations for Pre-Anesthesia Checkout Procedures*; this item should be performed by the provider even if it is part of the technician's workflow.

A more detailed daily pre-use check of the pipeline system may be part of institutional protocols. For example, a quick daily inspection of connections, supply hoses, gas pressures, and the presence of more than 90% oxygen in the inspiratory limb greatly minimizes risk. An important safety item on all machines is an audible and visual alarm that warns the operator of diminishing oxygen supply pressure. The only way to evaluate this safety device is to disconnect the wall oxygen supply and shut off the oxygen supply tank or tanks, in order to generate the alarm condition. The 2008 *Recommendations* do not mandate this maneuver.

Item 7: Verify That Vaporizers Are Adequately Filled and, If Applicable, That the Filler Ports Are Tightly Closed

Responsible parties: Provider (and technician if redundancy desired)

The anesthesia provider should verify that there is an adequate supply of anesthetic agent in the vaporizer if an inhaled anesthetic is planned. Because not every anesthetic utilizes an inhaled agent, alarm defaults may not include a low agent alarm. The risk of light anesthesia and recall can be mitigated by checking agent levels prior to proceeding.

Loose caps on vaporizer filler ports may be a source of leaks when the vaporizer is on. Because the breathing system pressure and leak test (see Item 12 below) is carried out with the vaporizer off, this source of leak may go otherwise undetected. Some vaporizers are designed to automatically close when the filling adapter is removed. Although not part of the 2008 PAC guidelines, some manufacturers recommend a check of their machine's vaporizer interlock system, which, if present, prevents more than one vaporizer from being activated simultaneously.

Item 8: Verify That No Leaks Are Present in the Gas Supply Lines Between the Flowmeters and the Common Gas Outlet

Frequency: Daily and whenever a vaporizer is changed

Responsible party: Provider or technician

As discussed above, the low-pressure section of the anesthesia workstation, from the flow control valves, through the vaporizers, and to the common gas outlet, is the most vulnerable to leaks. Leaks in this section of the machine can be associated with hypoxemia or patient awareness under anesthesia.^{22,24}

Two areas of the low-pressure leak test deserve emphasis. First, some anesthesia workstations include an outlet check valve (see Fig. 22.1). The implication of this check valve is that positive pressure in the breathing circuit *cannot* be

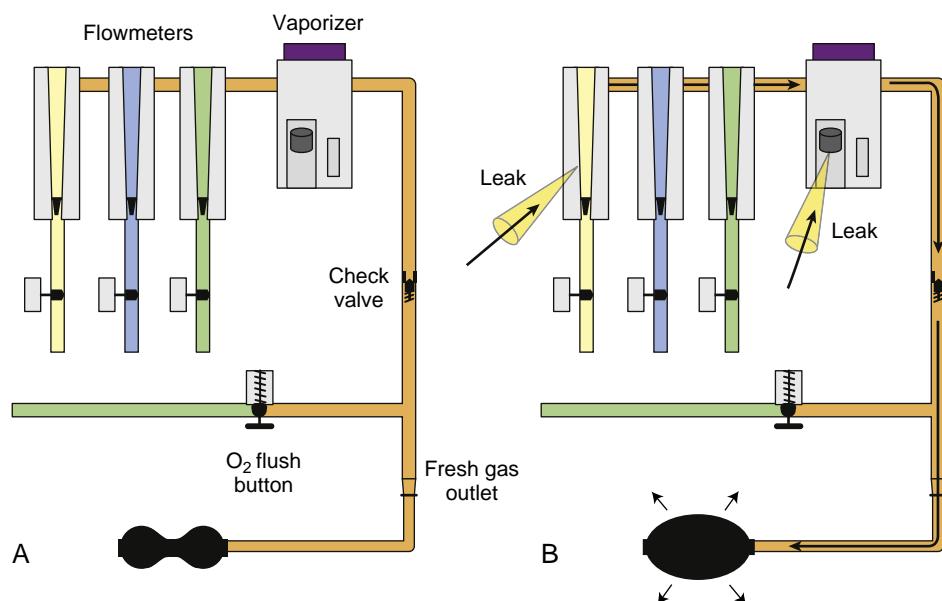


Fig. 22.56 The negative-pressure “universal” low-pressure system leak test. (A) A specially configured suction bulb is connected to the common (fresh) gas outlet and collapsed. Subatmospheric pressure is created in the low pressure circuit, thus opening the outlet check valve (if present) and exposing the vaporizers, tubing, and associated piping and connections to the vacuum. In a system without a leak, the bulb stays deflated. (B) Leaks in the system draw in ambient air and cause the suction bulb to inflate. O_2 , Oxygen.

used to check for leaks upstream in the low-pressure system, because the pressure will not be transmitted past the check valve. On these machines, a negative pressure test must be performed. Second, most vaporizer leaks are not detected unless the vaporizer is on. Therefore a thorough low-pressure leak test can require testing multiple vaporizers, depending on machine configuration. Some workstations (Maquet anesthesia machines and GE Healthcare workstations) do perform automated vaporizer leak testing on their unique vaporizers (ADU vaporizer).

In machines with an outlet check valve, a negative-pressure test must be performed. The negative-pressure leak test is simple to perform and is highly sensitive, detecting leaks as small as 30 mL/min. This simple test requires that the flow control valves be fully closed to prevent any flow of gas into the low-pressure circuit. A specially configured suction bulb, which can either be constructed or obtained from the manufacturer, is then attached to the common gas outlet (Fig. 22.56). The bulb is then squeezed repeatedly until it is fully collapsed. If the bulb does not stay collapsed for a specified period of time, then air is being sucked by the bulb into the machine through a leak that will allow gas to escape when the machine is pressurized. The same maneuver is carried out with each vaporizer opened in turn to check for associated leaks.

The negative-pressure test *can* be performed on machines without a check valve. For this reason, the negative-pressure test is sometimes referred to as the “universal leak test.” Several mishaps have resulted from application of the wrong leak test to the wrong machine.²³¹⁻²³⁴ When in doubt, the negative-pressure test is therefore preferred. However, many of the newer-generation anesthesia machines do not have an accessible common gas outlet; therefore negative-pressure low-pressure system testing cannot be performed. On these machines, either manual positive-pressure testing of the low-pressure system (and vaporizers)

is performed during the pre-use checkout, or low-pressure testing is accomplished as part of an automated checkout feature. Note that the automated low-pressure test on some machines needs to be specifically selected.^{214j}

Item 9: Test Scavenging System Function

Frequency: Daily

Responsible party: Provider or technician

Evaluation of the scavenging system is a manual maneuver. No automated checks are conducted. A test of the scavenging system begins by checking the proper assembly and integrity of each component and connection within the system including the gas transfer tubes leading from the APL valve and the ventilator relief valve to the scavenging interface. In the case of many modern machines, a single transfer tube may lead from a compact breathing system to the scavenge interface. The integrity of the vacuum tubing leading from the wall outlet to the scavenging interface should also be checked.

To test a closed, passive scavenger system (as seen in Fig. 22.55A), one creates high flow within the breathing system by occluding the patient “Y-piece” (or short-circuiting the inspiratory and expiratory limbs of the breathing circuit with breathing hose), occluding the exhaust hose outlet on the scavenging interface, and ensuring that the flow of gas exits the system through the positive-pressure safety relief valve so excess pressure does not build up in the breathing circuit (e.g., <10 cm H₂O). To test a closed, active scavenger system (as seen in Fig. 22.55B), two steps are required. A check of positive-pressure relief is conducted as just described for the passive, closed scavenger. Some manufacturers recommend that the suction needle valve be turned off for this step. A check of negative-pressure relief is conducted by setting scavenge interface suction to a routine setting, turning off all flow control valves on the anesthesia

machine, and occluding inflow into the patient's breathing circuit at the patient's Y-piece (or short circuiting the inspiratory and expiratory limbs of the breathing circuit with breathing hose) and at the breathing bag mount. At this point, the breathing pressure gauge should indicate a negligible negative pressure (e.g., no lower than $-1.0\text{ cm H}_2\text{O}$). Generally speaking, the scavenging suction on active systems should be adjusted so the reservoir bag is never overinflated or underinflated, but it should remain slightly inflated during routine use. Because the volume of gas being passed into the scavenging system varies, it may be necessary to adjust the needle valve. Given the diversity of breathing systems, this check serves as another instance in which users must consider manufacturer-specified protocols when developing a local PAC.

Checking the function of an open, active system as seen in Fig. 22.54 is relatively simple compared with checking a closed, active system. After ensuring that all gas transfer tubes and the suction lines are properly connected, the scavenger suction needle valve is adjusted to place the flowmeter bobbin between the indicator lines. A positive-pressure test and a negative-pressure test are then conducted as described earlier.

Item 10: Calibrate, or Verify Calibration of, the Oxygen Monitor and Check the Low Oxygen Alarm

Frequency: Daily

Responsible party: Provider or technician

The oxygen concentration analyzer is one of the most important monitors on the anesthesia workstation. Older anesthesia workstations used a galvanic cell oxygen sensor located near the patient's breathing circuit inspiratory valve. These devices have a finite life span, which is inversely proportional to the amount of oxygen exposure.^{234a} They are also vulnerable to drift. Therefore daily verification of calibration (and recalibration, if necessary) is recommended. Newer anesthesia workstations rely on side-stream multi-gas analyzers to measure the inspired oxygen concentration. The multi-gas analyzer is an irremovable and permanent component of the workstation. Thus it fulfills the requirement imposed on the manufacturer to provide inspired oxygen concentration monitoring. These monitors do not require daily calibration. Nevertheless, the function of the sensor should be checked in room air, to verify that it reads 21%.

The function of the low-oxygen concentration alarm should be tested daily. This may be done by manually setting the low oxygen concentration alarm limit to more than 21% while exposing the analyzer to room air, generating the alarm condition. A prudent default setting would be somewhere between 25% and 30%, unless oxygen concentrations lower than this value are used routinely. In any case, it is wise to keep it set to at least 21%. These steps may be carried out by a technician, according to local protocols.

Item 11: Verify Carbon Dioxide Absorbent Is Not Exhausted

Frequency: Before each use

Responsible party: Provider or technician

In order to utilize rebreathed gas, the anesthesia circle system requires a CO_2 absorber. Prior to each anesthetic, the absorbent should be assessed for exhaustion.

It is important for providers to know that absorbent color change is not as reliable as is the presence of *inspired* CO_2 on capnography in identifying exhausted absorbent. Capnometry should be used with every anesthetic that uses the circle system, and the provider should be vigilant for inspired CO_2 concentration greater than 0. A normal-appearing but nonfunctional absorbent is difficult to detect during the pre-use checkout procedure. It is no longer advised for providers to breathe in and breathe out of the breathing circuit manually to assess the functionality of the absorbent before a case.

Item 12: Breathing System Pressure and Leak Testing

Frequency: Before each use

Responsible parties: Provider and technician

This PAC item verifies that positive pressure can be developed and sustained in the breathing circuit, and that the APL ("pop-off") valve properly relieves pressure in the circuit. It is not rare for either the disposable breathing circuit components or the fixed anesthesia machine components to leak. Therefore a leak check of the breathing system is of paramount importance. Traditionally, this test has been performed manually after an inspection of the breathing circuit, removal of the gas sampling line, and capping of the gas sampling line port. With the machine set in the "bag" or the manual mode of ventilation, the gas flows are set to zero, the APL valve is closed, the patient's Y-piece is occluded, and breathing system is pressurized with the O_2 flush button to approximately $30\text{ cm H}_2\text{O}$ (Fig. 22.57). The circuit passes the leak test if it holds this pressure for at least 10 seconds. A decrease in pressure during the test should prompt a check of all plug-in, push-fit, and screw connectors, the seal of the absorber canister, and a careful inspection of the disposable tubing. One of the most common locations of a circuit leak is at the absorber canister, and it is particularly important for the anesthesia provider to apply this check rigorously immediately after the absorbent has been changed.

On many modern anesthesia machines, breathing circuit leak testing is an automated feature, although manual steps are still required for test preparation. Circuit compliance is often also automatically assessed on some machines during this phase to guide ventilator tidal volume delivery. Therefore the test should be performed with the circuit that is going to be used. The automated circuit leak test may be performed by a technician, but its completion should be verified by the provider. The importance of the leak test, on which depends the ability to deliver positive pressure ventilation, implies that it must be the provider's responsibility.

The APL valve should also be assessed at this time by opening it widely after the pressure test and ensuring that the breathing circuit pressure decreases rapidly to zero. A prompt pressure drop should occur regardless of APL valve design. The ability of the pressure-limiting type APL valve to maintain stable circuit pressure can be easily assessed, if required, by setting the APL valve to $30\text{ cm H}_2\text{O}$, occluding the patient's Y-piece in a manual mode of ventilation, increasing gas flow to approximately 5 L/min , and ensuring the circuit pressure, once stable, remains within a range close to that set on the APL valve.

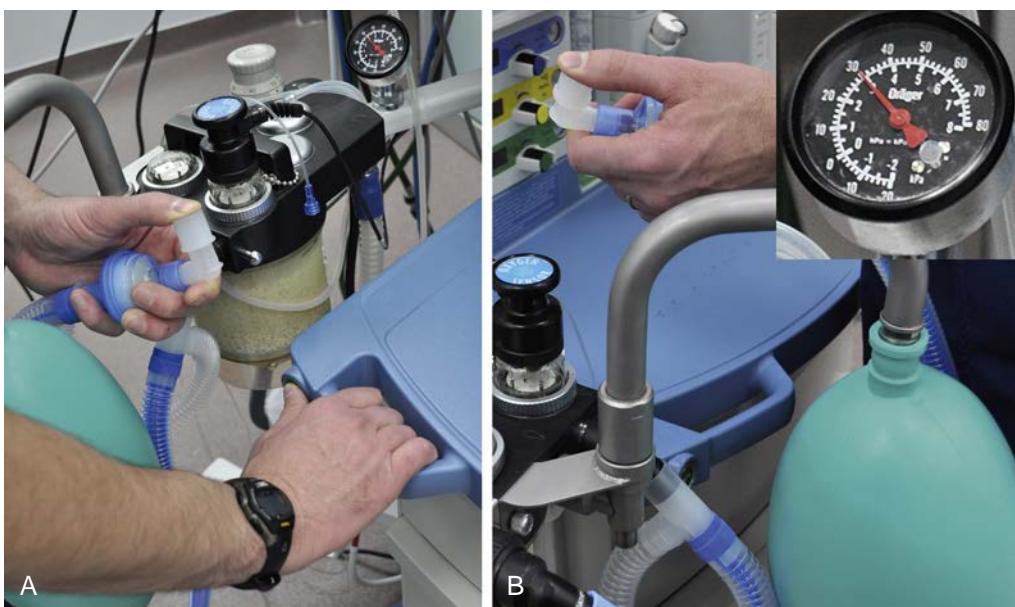


Fig. 22.57 Manual breathing system pressure and leak testing. Breathing system pressure and leak testing should be performed with the circuit configuration that will be used during anesthetic delivery. (A) The patient Y-piece or elbow is occluded, and the oxygen flush button is used to pressurize the breathing circuit to approximately 30 cm H₂O. (B) The circuit should hold pressure at this level for at least 10 seconds. It is important to ensure that the gas flows are set to zero (or their minimal values), the gas sample line is removed, and its circuit port is occluded.

Item 13: Verify That Gas Flows Properly Through the Breathing Circuit During Both Inspiration and Exhalation

Frequency: Before each use

Responsible parties: Provider and technician

This item assesses the circle breathing system for unobstructed flow and proper function of the unidirectional valves. This test of circuit flow is easily accomplished by placing a “test lung” or an extra breathing bag at the patient Y-piece. In the “bag” or a manual mode of ventilation, the operator ventilates the artificial “lung” with the breathing bag, then actively “exhales” (squeezes) the test lung back to the breathing bag in a to-and-fro motion (Fig. 22.58). This is the so-called *flow test*. The inspiratory valve should open and the expiratory valve should close during inspiration, and vice versa for exhalation. Obstruction to inspiratory flow during the flow test manifests as a “tight” breathing bag on “inspiration,” whereas expiratory limb obstructions cause impeded “exhalation.” Some form of flow test should be conducted because leak testing does not reliably identify circuit obstruction or unidirectional valve malfunction. Undetected circuit obstructions are particularly ominous and can manifest dramatically and sometimes immediately following induction.^{147,148,150} Subtle circuit obstruction may not be appreciable except by capnometry.

Automated machine checks may not assess for (or detect) obstruction to flow within the breathing circuit. A number of complications and near-misses involving an obstructed breathing circuit have been reported despite the performance of the automated circuit check.^{9,231,234b,234c} Although most user’s manuals for machines that perform automated aspects of the pre-use checkout describe a leak test function, few specifically describe a flow test or an assessment of unidirectional valve function. In fact, some modern machines that incorporate automated checkout

steps, including a leak test, recommend a manual assessment of the inspiratory and expiratory valves.^{214,31a} In the experience of this chapter’s authors, a full checkout procedure with test lung is uncommon in this era of automated machine checks. If this test is omitted, providers must be cognizant of the fact that unidirectional valve malfunction and breathing circuit obstruction have not been ruled out before starting the case.

Item 14: Document Completion of Checkout Procedures

Responsible parties: Provider and technician

Documentation of completion of the anesthetic checkout procedure by *providers* should occur within the anesthetic record. Currently, no guidance is available regarding where anesthesia or biomedical technician documentation of checkout procedures should occur. However, it would be prudent to maintain a detailed departmental log as a quality assurance tool.

Item 15: Confirm Ventilator Settings and Evaluate Readiness to Deliver Anesthesia Care (Anesthesia Time Out)

Frequency: Immediately before initiating the anesthetic regimen

Responsible parties: Provider

The authors of the 2008 *Recommendations* include as the last step in the PAC an “anesthesia time out.” The time out asks the anesthesia provider to confirm 6 items:

- Monitors functional?
- Capnogram present?
- Oxygen saturation by pulse oximetry measured?
- Flowmeter and ventilator settings proper?
- Manual/ventilator switch set to manual?
- Vaporizer(s) adequately filled?^{11b}

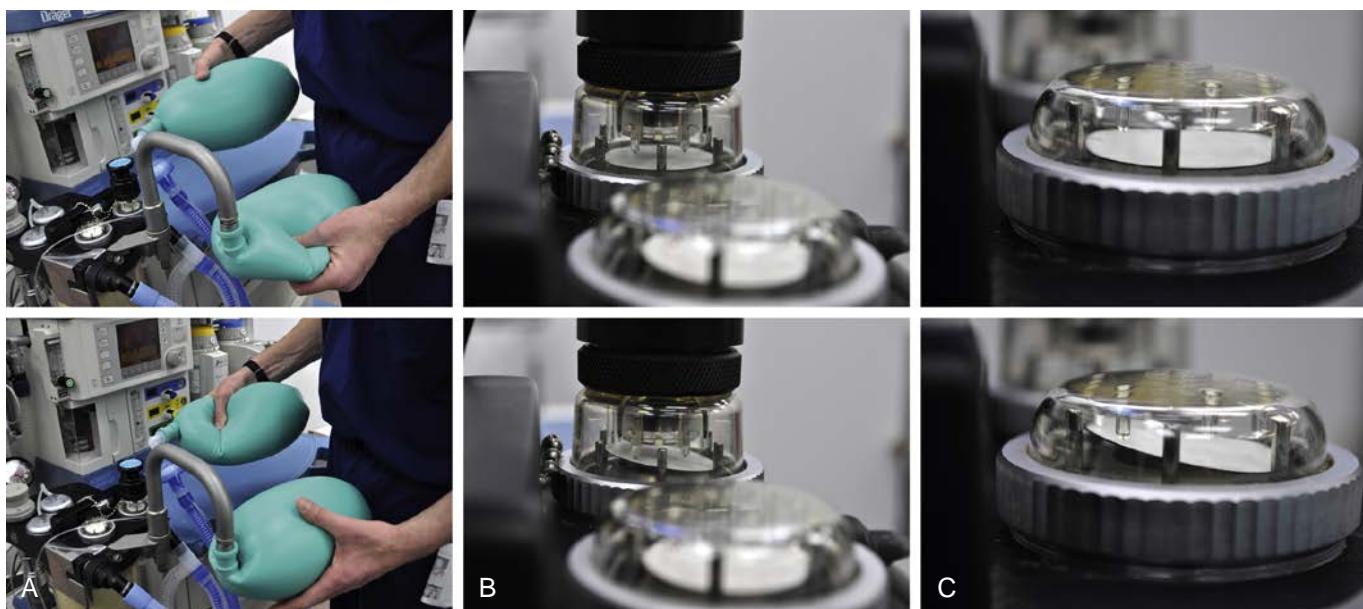


Fig. 22.58 (A-C) Verification that gas flows properly through the breathing circuit during both inspiration and exhalation with the to-and-fro “flow test.” Top row, A test lung or second reservoir bag is placed on the patient elbow piece. A squeeze of the breathing bag should cause flow through the inspiratory limb, open the inspiratory valve, fill the test lung, and hold the expiratory valve closed. Bottom row, A reciprocal squeeze of the test lung should cause flow through the expiratory limb, open the expiratory valve, fill the breathing bag, and hold the inspiratory valve closed. Circuit flow during the test should be smooth and unimpeded.

This last step serves as a recommended final preinduction check list of the machine and other important items including the application of essential monitors. Verifying appropriate ventilator settings is an important safety check, especially in practices with mixed adult and pediatric cases. Many contemporary anesthesia workstations can be programmed to offer adult and pediatric “profiles” that adjust the anesthesia ventilator’s default tidal volume and respiratory rate. Some older machines are more likely to retain the previous patient’s settings, with the potential for under- or over-ventilation. Spending time adjusting ventilator settings in the immediate postinduction period can be distracting.

The checklist above focuses on the anesthesia workstation but does not include other key equipment such as medications, intubation supplies, monitoring transducers, etc. Some providers rely on final check mnemonic devices such as the MS MAIDS checklist (Box 22.5). Regardless of the specific steps, a final checklist that verifies the presence and function of key safety items is fundamental to the safe delivery of anesthesia.

Additional Comments Pertaining to the ASA’s Pre-Anesthesia Checkout Procedure Recommendations (2008)

Although the 2008 PAC procedures are comprehensive, several steps that were part of the earlier PAC recommendations^{228,235} did not appear in the current recommendations. Some of these are still found in machine user’s manuals. The use of these steps should be based on local needs or requirements because the 2008 recommendations are not restrictive nor intended to be limiting. Some of these items are:

1. Disconnecting the central oxygen supply line to assess the low-oxygen supply pressure alarm and to purge the tank pressure gauges to zero

BOX 22.5 The MS MAIDS Checklist*

- **Machine:** The machine checkout is complete; the vaporizers are filled, closed, and set to “0”; all gas flows knobs are set to zero flow; the ventilator and pressure settings are appropriate for the upcoming patient, with the machine in manual/spontaneous breathing mode, and the adjustable pressure-limiting valve is open.
- **Suction:** Patient suction is adequate to clear the airway.
- **Monitors:** All required standard monitors are present and ready to go.
- **Airway:** Primary airway equipment and appropriate backup equipment are ready to go.
- **Intravenous:** Intravenous lines, fluids, and associated equipment are ready to go.
- **Drugs:** All necessary medications are available and are properly labeled.
- **Special:** Any special or unique items (i.e., additional monitors) required for the case are available and ready.

*An example mnemonic for an “Anesthesia Time Out,” which ensures that all appropriate checks have been completed, all essential equipment is available, and the machine is properly configured for the next patient.

2. Inspecting the gas supply hoses for cracks or wear
3. Testing the flowmeters for smooth operation
4. Testing the proportioning system by attempting to create a hypoxic oxygen–nitrous oxide mixture

AUTOMATED ANESTHESIA MACHINE CHECKOUT PROCEDURES

Important points to consider regarding automated PAC features or “self-tests” are that (1) they differ between manufacturers and models; (2) it is sometimes difficult to determine precisely which segments or components are actually being checked by reading the user’s manual, and (3) no machine

automatically checks all the items on an effective PAC. At least some manual steps are required. Investigators have suggested that many providers do not understand exactly what is being checked by automated checks, or they make false assumptions regarding their respective machine's automated checkout procedure. It is easy to understand why the authors of the ASA's 2008 *Recommendations for Pre-Anesthesia Checkout Procedures* warned about an overreliance on the automated machine checkout. For example, one manufacturer's self-test screen reports a "leakage" amount, but the display or manual does not specify which section is responsible (e.g., the breathing circuit or the LPS). The operator must make an assumption that the low-pressure system is also being tested for leaks, and the manual does not state that any vaporizer should be turned "on" during leak testing. Finally, it was not clear in this manual whether the circuit is assessed for proper unidirectional flow or obstruction. When developing a local PAC procedure, providers should gain familiarity with their machine's automated checkout procedure through the user's manual. If an important item is not actually part of the described self-check or is not suggested in the user's manual, it should not be assumed that it can be neglected. Not requiring that conventional vaporizers be opened during a leak test of the low-pressure system is such an example.

MACHINE-EMBEDDED PREANESTHESIA MACHINE CHECKOUT CHECKLISTS

Some anesthesia machines have embedded PAC checklists, which are displayed during machine checkout. Like their paper counterparts, they help guide users through manual and self-test functions. If an embedded checklist provides a complete solution for a department, then it can be used exclusively. However, local requirements may exceed or depart from the embedded checklist. In these cases, the use of the embedded checklist (or a modification thereof) can become a line item within the local PAC checklist.

DEVELOPING A LOCAL PREANESTHESIA MACHINE CHECKOUT CHECKLIST

The goal of a PAC is to evaluate and configure the anesthesia workstation properly so it performs its functions safely and smoothly. The objectives of the PAC checklist are to guide the operator through an effective PAC and to promote compliance through ease of use. A PAC checklist can also serve as a quality control tool by codifying important items onto an organized list used by all providers.²³⁶ The checkout procedure should be ergonomically ordered to minimize redundant movements and save time by placing procedures in a rational sequence.²³⁷ Finally, the checklist should be as short as possible, yet be detailed enough so critical items are not omitted.

Acknowledgment

The editors and publisher would like to thank Drs. Steven G. Venticinque and J. Jeffrey Andrews for contributing a chapter on this topic in the prior edition of this work. It has served as the foundation for the current chapter.



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KEY POINTS

- The introduction of thiopental into clinical practice in 1934 marked the beginning of modern intravenous (IV) anesthesia. Today, IV anesthetics are used for induction and maintenance of anesthesia and sedation in a wide variety of circumstances.
- The most commonly used IV anesthetic is propofol, an alkylphenol presently formulated in a lipid emulsion. Propofol provides rapid onset and offset with context-sensitive decrement times of approximately 10 minutes when infused for less than 3 hours and less than 40 minutes when infused for up to 8 hours. Its mechanism of action is likely the enhancement of gamma-aminobutyric acid (GABA)-induced chloride currents. Propofol causes a dose-dependent decrease in arterial blood pressure predominantly through a decrease in systemic vascular resistance and causes moderate respiratory depression. A unique action of propofol is its antiemetic effect, even at concentrations less than those producing sedation. A growing body of evidence suggests propofol may have antitumor potential.
- Barbiturates were the most commonly used IV drugs administered to induce anesthesia prior to the introduction of propofol. Thiopental provides rapid onset and offset when used as a single dose, but it accumulates rapidly with repeated or prolonged administration thus postponing recovery from anesthesia. Methohexitol has a rapid onset and offset similar to propofol for procedures lasting less than 2 hours. The barbiturates are administered as sodium salts diluted in a water base at an alkaline pH. Similar to propofol, the barbiturates provide their hypnotic effects largely through action on the GABA receptor. Barbiturates provide cerebral protection and are, apart from induction of anesthesia, used primarily for this purpose. They cause a moderate dose-dependent decrease in arterial blood pressure (primarily as a result of peripheral vasodilation) and respiratory drive. The barbiturates are contraindicated in patients with porphyria.
- The benzodiazepines are used primarily for anxiolysis and amnesia or for conscious sedation. The water-soluble benzodiazepine midazolam is most frequently used intravenously because of its rapid onset and offset compared with other benzodiazepines (e.g., diazepam). The onset time of midazolam is slower than that of propofol and barbiturates, and its offset, especially with larger doses or a prolonged infusion, is considerably longer than that of propofol or methohexitol and may be prolonged in hepatic and renal failure. The benzodiazepines act through the GABA receptor. Flumazenil is a specific benzodiazepine antagonist. It can be used to reverse the effects of benzodiazepines but should be used with caution because its antagonizing effect often lasts shorter than the benzodiazepine effect that it is supposed to antagonize. The benzodiazepines generally produce only a mild decrease in arterial blood pressure and mild-to-moderate respiratory depression. Remimazolam is the most recent benzodiazepine with an ultrashort duration of action due to its rapid clearance through plasma esterases.
- Ketamine is a phencyclidine derivative that acts primarily, but not entirely, as antagonist of the N-methyl-D-aspartate (NMDA) receptor. It produces a dissociative state of hypnosis and analgesia. It has been used for induction and maintenance of anesthesia. Ketamine is associated with significant adverse psychological effects from larger doses and has several other side effects. It is used now primarily for its analgesic properties. It has rapid onset and relatively rapid offset, even after an infusion of several hours. It has sympathomimetic effects that preserve cardiac function. Ketamine has minimal effect on respiration and tends to preserve autonomic reflexes. In addition, ongoing research suggests ketamine may play a role as an antidepressant.
- Etomidate is an imidazole derivative used primarily for induction of anesthesia, especially in elderly patients and patients who are cardiovascularily compromised. It has a rapid onset of effect and a rapid offset even after a continuous infusion. A dose used to induce anesthesia results in inhibition of adrenocortical synthesis and possible mortality in intensive care unit (ICU) patients. The major advantage of etomidate is its minimal effect on the cardiovascular and respiratory systems.
- Dexmedetomidine is the most recently released IV anesthetic. It is a highly selective α_2 -adrenergic agonist that produces sedation, sympatholysis, hypnosis, and analgesia. Dexmedetomidine is approved for ICU sedation of initially intubated and mechanically ventilated patients, up to 24 hours. It may be advantageous for its ability to prevent delirium. Its second indication is procedural sedation of nonintubated patients. With increasing frequency dexmedetomidine finds its use as a sedative during invasive or radiological procedures and as an adjunct in central or peripheral neural blockade. Its primary action is as an agonist on α_2 -receptors in the locus caeruleus. It has minimal effect on respiration. Heart rate and cardiac output show a concentration-dependent decrease.

■ Droperidol, a butyrophenone and major tranquilizer, was initially used to produce a state of neuroleptanesthesia. Its prolongation of the QT interval has resulted in its withdrawal in several countries and its limitation to the treatment of postoperative nausea and vomiting (PONV) with a black box warning in the United States. Because the use of low-dose droperidol (<1.25 mg) for PONV has not been approved by the US Food and Drug Administration (FDA), the black box warning does not relate to this use. Clinically significant prolongation of the QT interval by doses used for PONV (0.625 to 1.25 mg) has been challenged by several editorials, and this effect has not been substantiated by review of the reported cases or other literature. Low-dose droperidol remains an effective antiemetic therapy and is used as such in many European countries (also see Chapter 80).

Intravenous (IV) anesthesia can be traced back to 1656 with Percival Christopher Wren's and Daniel Johann Major's first experiments with the IV using a goose quill and bladder to inject wine and ale into a dog's vein. In 1665 German naturalist and physician Sigismund Elsholz made the first attempt at IV anesthesia in humans and investigated the possibilities of IV injection with opiates. IV anesthesia further evolved when Fedoroff started using hedonal in St. Petersburg in 1905 and entered the era of modern anesthesia with the release of thiopental in 1936.¹ Since these beginnings, and in particular during the past three decades, the pharmacokinetics and pharmacodynamics of IV anesthetics and their interactions have been described in increasingly greater detail. This body of knowledge and the availability of increasingly shorter-acting drugs now allow the anesthesia provider to administer anesthesia not on the basis of the needs of the population but to focus anesthesia on the individual needs of the patient. Today's anesthesia provider is supported by modern IV drug administration techniques like target-controlled infusion and central nervous system (CNS) monitoring devices to further optimize and individualize the application of IV anesthesia. This chapter describes the current status of the pharmacology of IV anesthetics and their place in modern anesthesia.

Propofol

HISTORY

Since its introduction in the 1970s, propofol has become the most used IV hypnotic today. Building on work on the sedative properties of phenol derivates in mice, propofol was developed in the United Kingdom by Imperial Chemical Industries as ICI 35868. The initial solution of propofol, as released in 1977 in Cremophor EL,² was withdrawn because of anaphylactic reactions, and replaced and reformulated as an emulsion of a soya oil/propofol mixture in water and relaunched in 1986. Propofol is used for induction and maintenance of anesthesia and for sedation in and outside the operating room.

PHYSICOCHEMICAL CHARACTERISTICS

Propofol (Fig. 23.1) is one of a group of alkylphenols that were explored for their hypnotic properties in animals.³⁻⁵ The alkylphenols are highly lipid soluble and are insoluble in an aqueous solution.⁶ Numerous formulations of propofol are marketed today. The formulation most used is that of

1% propofol, 10% soybean oil, and 1.2% purified egg phospholipid added as emulsifier, with 2.25% of glycerol as a tonicity-adjusting agent, and sodium hydroxide to change the pH. Following concerns regarding microbial growth in the emulsion, EDTA was added for its bacteriostatic activities. Propofol has a pH of 7 and appears as a slightly viscous, milky white substance, a result of small lipid droplets in solution. In Europe, a 2% formulation and a formulation in which the emulsion contains a mixture of medium-chain and long-chain triglycerides also are available. All formulations commercially available are stable at room temperature, are not light sensitive, and may be diluted with 5% dextrose in water. Propofol concentrations may be measured both in whole blood and in the exhaled air.⁷⁻¹⁰

In December 2008 the US Food and Drug Administration (FDA) approved fospropofol disodium (Lusedra) for monitored anesthesia care in adult patients undergoing diagnostic and therapeutic procedures. Fospropofol is a water-soluble prodrug of propofol that is metabolized by alkaline phosphatases in the liver to the active metabolite propofol. One millimole (mmol) of propofol is generated for each mmol of fospropofol sodium administered. About 1.86 mg of fospropofol sodium is the molar equivalent of 1 mg propofol. In April 2010, six studies on the pharmacokinetics and pharmacodynamics of fospropofol were retracted as a result of an analytical assay inaccuracy that was discovered after publication of these studies.^{11,12} Since then, few data on the pharmacokinetics and pharmacodynamics of fospropofol have been published. Although fospropofol remains available for monitored anesthesia care, data now available are scarce and most pharmacokinetic-pharmacodynamic data that are available come from the United States as described in a recent review.¹³ In contrast to propofol, fospropofol is not associated with pain on injection, although mild to moderate perineal paresthesias and pruritis minutes after a bolus injection of fospropofol have been reported and may be due to a phosphate metabolite.

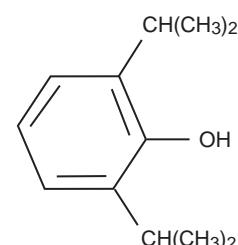


Fig. 23.1 Structure of propofol, an alkylphenol derivative.

PHARMACOKINETICS

Propofol is oxidized to 1,4-diisopropyl quinol in the liver. Propofol and 1,4-diisopropyl quinol are conjugated with glucuronic acid to propofol-1-glucuronide, quinol-1-glucuronide, and quinol-4-glucuronide, which then may be excreted by the kidneys.^{14,15} After a 2.5-hour anesthetic with propofol, patients excrete propofol and propofol metabolites for over 60 hours.¹⁵ Less than 1% propofol is excreted unchanged in urine, and only 2% is excreted in feces. The metabolites of propofol are thought to be inactive. Because clearance of propofol (>1.5 L/min) exceeds hepatic blood flow, extrahepatic metabolism or extrarenal elimination may occur. Extrahepatic metabolism has been confirmed during the anhepatic phase of patients receiving a transplanted liver with the determination of propofol metabolites after propofol administration in the absence of liver tissue. The most important extrahepatic site for propofol metabolism is the kidney.^{16,17} Renal metabolism of propofol accounts for up to 30% of propofol clearance, which explains the rapid clearance of propofol, which exceeds liver blood flow. The lungs also may play a role in the extrahepatic propofol metabolism.^{18,19} In sheep, the lungs are responsible for approximately 30% of the uptake and first-pass elimination after a bolus dose. In humans, a 20% to 30% decrease in propofol concentration measured across the lung exists with a higher concentration of the metabolite 2,6-diisopropyl 1,4-quinol on the arterial side of the circulation.

Propofol is generally known for its hemodynamic depressant effects and may reduce hepatic blood flow. As such, it may reduce the clearance of other drugs metabolized by the liver, in particular those with a high extraction ratio.²⁰ In addition, propofol is known as a CYP3A4 inhibitor.²¹ In contrast to enzyme induction that may take several days or weeks to develop, competitive inhibition of CYP activity may occur almost instantaneously due to the competition of two drugs (e.g., propofol and midazolam) for the enzyme's active site. A short-term exposure to propofol at a blood concentration of 3 µg/mL already reduces the CYP3A4 activity by about 37%.

Fospropofol^{22-28,28a} is a water-soluble prodrug of propofol and is chemically described as phosphono-O-methyl-2,6-diisopropylphenol, disodium salt ($C_{13}H_{19}O_5PNa_2$). Fospropofol is metabolized by alkaline phosphatases to propofol, formaldehyde, and phosphate. Formaldehyde is further metabolized to formate which is then eliminated, primarily by oxidation to carbon dioxide. Over 71% of fospropofol is recovered in the urine within 192 hours following a single 400 mg IV dose. Renal elimination is <0.02% and total body clearance in the order of 0.28 L/h/kg. The terminal elimination half-life of fospropofol is 0.88 hours. The pharmacokinetics of fospropofol and liberated propofol are not affected by race, sex, or mild to moderate renal impairment. Furthermore, fospropofol pharmacokinetics are not affected by age or alkaline phosphatase concentration. So far, no pharmacokinetic interactions have been found between fospropofol and fentanyl, midazolam, morphine, or with propofol. This is probably because fospropofol is not subject to cytochrome P450 enzyme mediated metabolism.¹³

The pharmacokinetics of propofol have been described by two-compartment and three-compartment models

TABLE 23.1 Pharmacokinetic Variables for Commonly Used Intravenous Anesthetics

Elimination	Elimination Half-Life (h)	Clearance (mL/kg/min)	Vd_{ss} (L/kg)
Dexmedetomidine	2-3	10-30	2-3
Diazepam	20-50	0.2-0.5	0.7-1.7
Droperidol	1.7-2.2	14	2
Etomidate	2.9-5.3	18-25	2.5-4.5
Flumazenil	0.7-1.3	5-20	0.6-1.6
Ketamine	2.5-2.8	12-17	3.1
Lorazepam	11-22	0.8-1.8	0.8-1.3
Methohexitol	2-6	10-15	1.5-3
Midazolam	1.7-2.6	6.4-11	1.1-1.7
Propofol	4-7	20-30	2-10
Thiopental	7-17	3-4	1.5-3

Vd_{ss} , Apparent volume of distribution at steady state.

From Reves JG, Glass P, Lubarsky DA, et al. Intravenous anesthetics. In: Miller RD, Eriksson LI, Fleisher LA, et al, eds. *Miller's Anesthesia*, 7th ed. Philadelphia: Churchill Livingstone; 2010: 719-768.

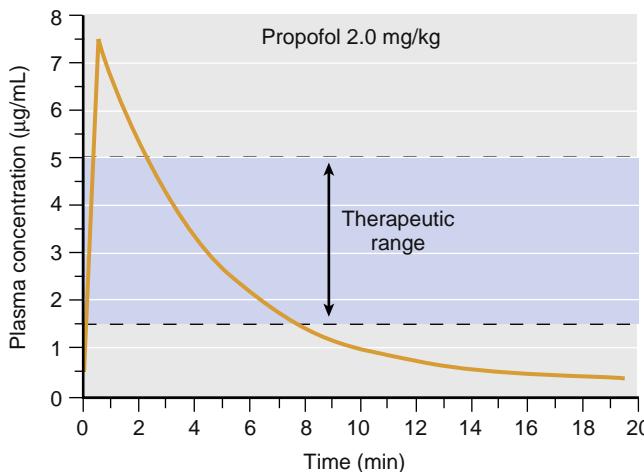


Fig. 23.2 Simulated time course of whole blood levels of propofol after an induction dose of 2 mg/kg. Blood levels required for anesthesia during surgery are 2 to 5 µg/mL, with awakening usually occurring at a blood level less than 1.5 µg/mL.

(Table 23.1).^{28b} After a single bolus dose, whole blood propofol levels decrease rapidly as a result of redistribution and elimination (Fig. 23.2). The initial distribution half-life of propofol is 2 to 8 minutes. Studies in which the disposition of propofol is described by a three-compartment model give initial and slow distribution half-lives of 1 to 8 minutes and 30 to 70 minutes and an elimination half-life of 4 to 23.5 hours.²⁹⁻³⁴ The context-sensitive half-time for propofol (Fig. 23.3) for infusions of up to 8 hours is less than 40 minutes.³⁵ Because the required decrease in concentration for awakening after anesthesia or sedation with propofol is generally less than 50%, recovery from propofol remains rapid even after prolonged infusion. The volume of distribution of the central compartment has been calculated between 6 and 40 L, and the volume of distribution at steady state has been calculated as 150 to 700 L. The

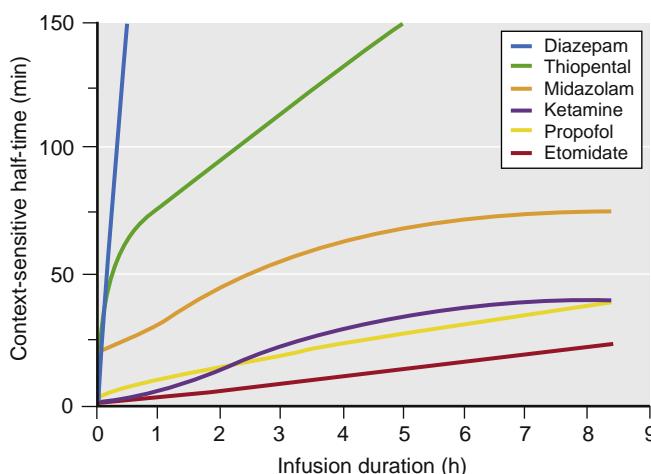


Fig. 23.3 The context-sensitive half-times for commonly used IV anesthetic drugs. The context-sensitive half-time is the time for the plasma level of the drug to decrease 50% after cessation of infusion. The duration of infusion is plotted on the horizontal axis. The rapidity with which the drug level decreases is directly related to the time of infusion (i.e., the longer the drug is infused, the longer the half-time). Etomidate, propofol, and ketamine have significantly shorter half-times than thiopental and diazepam, which makes them more suitable for prolonged infusion.

central compartment generally is smaller in the elderly as a result of the reduced cardiac output in these patients. A reduced cardiac output is associated with a higher peak plasma concentration, which is reflected by a smaller central compartment in the pharmacokinetic analysis. The clearance of propofol is extremely high—1.5 to 2.2 L/min. As discussed earlier, this exceeds hepatic blood flow, and extrahepatic metabolism has been shown.

The equilibrium constant for propofol based on suppression of the activity in the electroencephalogram (EEG) is about 0.3 min, and the half-life of equilibrium ($T_{1/2\text{keo}}$) between plasma concentration and EEG effect is 2.5 minutes. The time to peak effect is 90 to 100 seconds. The onset of EEG effect with propofol seems to be independent of age. The onset of decreasing arterial blood pressure is much slower (double the time) and increases with age.³⁶ For EEG and blood pressure changes, elderly patients show a concentration dependent increasing sensitivity. The pharmacokinetics of propofol may be altered by various factors (e.g., gender, weight, preexisting disease, age, and concomitant medication).³⁷⁻³⁹ Some studies suggest that propofol may exhibit nonlinear pharmacokinetics.⁴⁰ Because propofol has a high extraction ratio, this may impair its own clearance by decreasing cardiac output and thus hepatic blood flow.⁴¹ As a result, a doubling of the dose of propofol may lead to a drug concentration that may be more than twice that initially experienced. In contrast, an increase in cardiac output induced by sympathetic mimetic administration may lead to a decrease in the propofol plasma concentration. In a hemorrhagic shock model propofol concentrations increased 20% until uncompensated shock occurred, when there was a rapid and marked increase in propofol concentrations.⁴²

In term and preterm neonates, variability of propofol clearance was accounted for largely by postmenstrual and postnatal age with very fast maturation of clearance in neonatal life. Dosing in these neonates needs to be calculated

with extreme care.^{43,44} Women have a larger volume of distribution and higher clearance rates, but the elimination half-life is similar for males and females. Elderly individuals have decreased clearance rates and a smaller central compartment volume.⁴⁵ Both may be the result of a reduced cardiac output. Because of this and because of an increased sensitivity to the propofol effect in the elderly, patients aged 80 years or older generally need 50% of the propofol dose of patients aged 20 years old to target the same level of sedation or hypnosis.^{29,38,45,46} Children have a relatively larger central compartment volume (50%) and a more rapid clearance (25%).^{31,47} In children older than 3 years, volumes and clearances should be weight adjusted (also see Chapter 77). Children younger than 3 years of age also show weight-proportional pharmacokinetic parameters, but with larger central compartment and systemic clearance values than in adults or older children. This finding explains the larger dose requirements in this age group.^{48,49} Hepatic disease seems to result in larger steady state and central compartment volumes; clearance is unchanged, but the elimination half-life is slightly prolonged, as is time to recovery.^{50,51} In clinical practice, no significant dose adjustment is required in case of hepatic disease. The extrahepatic clearance of propofol that may compensate for a reduced hepatic function may be responsible for this.

Midazolam affects the pharmacokinetics of propofol.⁵² In the presence of a sedative midazolam concentration of 200 ng/mL, the blood propofol concentrations become elevated by about 25%. Midazolam reduces propofol metabolic clearance from 1.94 to 1.61 L/min, Cl_2 from 2.86 to 1.52 L/min, and Cl_3 from 0.95 to 0.73 L/min. The high extraction ratio of propofol of 0.79 to 0.92 suggests that the metabolic clearance of propofol may not be affected by enzyme inhibition but may be susceptible to changes in hepatic perfusion. The changes in the pharmacokinetics of propofol induced by midazolam thus may be the result of the hemodynamic alterations induced by the coadministration of midazolam.

Propofol in its turn affects midazolam pharmacokinetics as well.²⁰ In the presence of sedative concentrations of propofol, plasma midazolam concentrations increased by 27%. In the presence of propofol, midazolam is administered in a smaller central compartment from which midazolam is cleared and distributed less rapidly to peripheral tissues. For example, alfentanil⁵³ has been shown to increase blood propofol concentrations through a reduction in the elimination and distribution clearance of propofol. This is in line with other pharmacokinetic interactions between hypnotics and opioids when combined with propofol. Propofol has been shown to increase alfentanil concentrations by decreasing the elimination and the rapid and slow distribution clearances of alfentanil. Coadministration of propofol increased remifentanil concentrations via both a decrease in the central volume of distribution and distributional clearance of remifentanil by 41% and elimination clearance by 15%. Propofol kinetics is unaltered by renal disease.

As previously stated, pharmacokinetic data on the disposition of fospropofol are scarce. Phase I and phase II studies were conducted in Europe when a detection error became apparent resulting in the retraction of six published manuscripts. Currently, no further pharmacokinetic studies have been initiated. The pharmacokinetics of fospropofol in humans remains largely unknown.

Fospropofol protein binding is extensive (98%).¹³ It has a small volume of distribution of 0.3 L/kg, a total body clearance of 0.36 L/kg/h with a terminal elimination half-life of 0.88 hours. After a bolus dose of 6 mg/kg of fospropofol, the parent drug peaks at 4 minutes and is rapidly metabolized to propofol with a peak plasma propofol concentration at 12 minutes after administration of fospropofol. With this fospropofol dose the highest plasma concentration reached (C_{max}) of fospropofol was 78.7 µg/mL and the C_{max} of propofol was 1.08 µg/mL. The total body clearance of fospropofol and propofol were 0.36 and 3.2 L/kg/h. The terminal half-lives were 0.88 and 1.13 hours, respectively.

Pharmacodynamics

EFFECTS ON THE CENTRAL NERVOUS SYSTEM

The hypnotic action of propofol is mostly mediated by enhancing γ-aminobutyric acid (GABA)-induced chloride current through its binding to the β-subunit of GABA_A receptor. Sites on the β₁-subunit, β₂-subunit, and β₃-subunit of the transmembrane domains are crucial for the hypnotic action of propofol.^{54,55} The α₁-subunit and γ₂-subunit subtypes also seem to contribute to modulating the effects of propofol on the GABA receptor. The effect of propofol has been described in two manners—indirect and direct. Propofol exhibits an indirect effect by potentiation of the ion channel activation by GABA, shifting the concentration-response relationship to the left. At higher propofol concentrations, propofol is also thought to directly activate GABA_A receptor channels.⁵⁶⁻⁵⁸ The exact mechanism and location of changes that are associated with the change from consciousness to the unconscious state are not yet fully understood. Some experts suggest that a proper functioning of the brain stem-thalamo-cortical arousal circuits are critical while others state that consciousness is more related to fronto-parietal association cortex activity. Propofol, through its action on GABA_A receptors⁵⁹ in the hippocampus, inhibits acetylcholine release in the hippocampus and prefrontal cortex. The α₂-adrenoreceptor system also seems to play an indirect role in the sedative effects of propofol.⁶⁰ Resting state fMRI studies suggest that propofol's action may be related to a CNS that reduces its discriminable state and switches into stereotypical patterns of firing under propofol sedation.⁶¹ The so called default mode network (DMN), including the posterior cingulated, the medial frontal cortex, and bilateral parietal cortices, is the anatomical substrate in which these stereotypical patterns become visible. Using positron emission tomography, propofol hypnosis is related with reduced activity in the thalamic and precuneus regions. These regions likely play an important role in propofol-induced unconsciousness.⁶²

Propofol results also in widespread inhibition of the N-methyl-d-aspartate (NMDA) subtype of glutamate receptor through modulation of sodium channel gating, an action that also may contribute to the drug's CNS effects.^{63,64} Propofol has a direct depressant effect on neurons of the spinal cord. In acutely dissociated spinal dorsal horn neurons, propofol acts on GABA_A and glycine receptors.⁶⁵ The sense of well-being in patients with propofol is related to the increase in dopamine concentrations in the

nucleus accumbens (a phenomenon noted with drugs of abuse and pleasure-seeking behavior).⁶⁶ Propofol's antiemetic action may be explained by the decrease in serotonin levels it produces in the area postrema, probably through its action on GABA receptors.⁶⁷

The onset of hypnosis after a dose of 2.5 mg/kg is rapid (one arm–brain circulation), with a peak effect seen at 90 to 100 seconds. The median effective dose (ED₅₀) of propofol for loss of consciousness is 1 to 1.5 mg/kg after a bolus. The duration of hypnosis is dose-dependent, being 5 to 10 minutes after 2 to 2.5 mg/kg. Age markedly affects the induction dose, which is largest at ages younger than 2 years (ED₉₅ 2.88 mg/kg) and decreases with increasing age. This is a direct result of the altered pharmacokinetics in children and elderly. Children exhibit a relatively larger central compartment and therefore need a higher dose to assure a similar blood-drug concentration.⁶⁸⁻⁷⁰ In addition, the rapid clearance of propofol in children requires a larger maintenance dose as well. Increasing age decreases the propofol concentration required for loss of consciousness.

At subhypnotic doses, propofol provides sedation and amnesia. Propofol infusions of at least 2 mg/kg/h were necessary to provide amnesia in unstimulated volunteers. Awareness during surgery at higher infusion rates has been reported. During surgical procedures, extremely high infusion rates producing blood propofol concentrations in excess of 10 µg/mL may be necessary to prevent awareness if propofol is used as the sole anesthetic. Propofol also tends to produce a general state of well-being. Hallucinations, sexual fantasies, and opisthotonus occur after propofol administration.

The effect of propofol on the EEG, as assessed after 2.5 mg/kg followed by an infusion, shows an initial increase in alpha rhythm followed by a shift to gamma and theta frequency. Rapid infusion rates produce burst suppression at blood propofol concentrations higher than 8 µg/mL. Propofol causes a concentration-dependent decrease in the bispectral index (BIS), with 50% and 95% of patients unable to respond to a verbal command at a BIS of 63 and 51, respectively. The propofol concentration at which 50% of volunteers failed to respond to verbal command was 2.35 µg/mL. Lack of recall was observed in 95% of patients at a BIS value of 77.⁷¹ Propofol effect site concentrations provide similar correlation with decreases in the spectral entropy variable derived from the EEG as it does with BIS, and a similar ability to titrate propofol anesthetic effect. The effect of propofol on epileptogenic EEG activity is controversial. Propofol may suppress seizure activity via GABA agonism, inhibition of NMDA receptors, and modulation of slow calcium ion channels. However, the same GABA agonism and glycine antagonism may also induce clinical seizures and EEG epileptiform changes.⁷² This especially may occur during induction of and emergence from anesthesia. Propofol has a dose-dependent anticonvulsant. Propofol has even been used to treat epileptic seizures. Yet propofol can cause grand mal seizures and has been used for cortical mapping of epileptogenic foci.⁷³

Unfortunately, propofol can be addictive. An important issue in the potential of abuse is the development of tolerance. Tolerance to a drug creates circumstances for abuse. Propofol is being used as a sedative in the intensive care unit (ICU); in 20% to 40% of patients, the propofol dosage

regimen needs to be repeatedly adjusted upward in order to maintain the same effect.⁷⁴ Data on propofol abuse in the general public are unknown but the incidence of abuse is likely to be low compared to other substances. For healthcare workers, propofol is easy to access and case reports of lethal self-administration do occur. Some have suggested that there are more frequent incidences of propofol abuse by healthcare providers^{75,76} and support stricter propofol regulation. In contrast to propofol, fospropofol was classified in 2009 by the US Drug Enforcement Administration (DEA) as a controlled substance.

Propofol decreases intracranial pressure (ICP) in patients with either normal or increased ICP (also see Chapter 57). The decrease in ICP (30% to 50%) is associated with significant decreases in cerebral perfusion pressure (CPP).⁷⁷ The use of propofol in head-injured patients should be restricted to doses providing mild-to-moderate sedation (i.e., blood concentration of 2 $\mu\text{g}/\text{mL}$, infusion of 25 to 75 $\mu\text{g}/\text{kg}/\text{min}$).⁷⁸ Anesthetics are neuroprotective because they reduce the metabolic oxygen use that is beneficial for the balance between energy supply and demand and because they increase the tolerance to hypoxia by the neuronal tissue. Propofol has no direct preconditioning effect but may attenuate glutamate-mediated excitotoxicity.⁷⁹⁻⁸¹ Propofol acutely reduces intraocular pressure by 30% to 40%. Compared with thiopental, propofol produces a larger decrease in intraocular pressure and is more effective in preventing an increase in intraocular pressure secondary to succinylcholine and endotracheal intubation. Normal cerebral reactivity to carbon dioxide and autoregulation are maintained during a propofol infusion.

The neuroprotective effects of propofol remain controversial.⁸² In an incomplete ischemia model in rats, propofol administered to burst suppression results in significantly better neurologic outcome and less brain tissue injury compared with fentanyl. Propofol administered at sedative concentrations started either immediately after or at 1 hour after an ischemic insult significantly reduced infarct size compared with awake controls infused with intralipid.^{83,84} Subanesthetic doses of propofol also induce neuroapoptosis in the infant mouse brain.⁸⁵ In addition, anesthetic doses of propofol in rats⁸⁶ induce complex changes that are accompanied by cell death in the cortex and thalamus of the developing rat brain. The neuronal protective effect of propofol may be due to the attenuation of changes in adenosine triphosphate, calcium, sodium, and potassium caused by hypoxic injury and its antioxidant action by inhibiting lipid peroxidation. Current evidence indicates that propofol can protect neurons against ischemic injury caused by excitotoxicity, but neuroprotection may be sustained only if the ischemic insult is relatively mild and is not sustained after a prolonged recovery period. Prolonged propofol sedation in children is associated with adverse neurologic sequelae.⁸⁷

Many anesthetic-related drugs decrease the required dose or blood concentrations of propofol's pharmacologic action. The "required dose" is usually directly related to the required concentration for a given effect. The propofol Cp_{50} (blood concentration needed for 50% of subjects to not respond to a defined stimulus) for loss of response to verbal command in the absence of any other drug is 2.3 to 3.5 $\mu\text{g}/\text{mL}$.⁸⁸⁻⁹⁰ The propofol Cp_{50} to prevent movement on skin incision is 16 $\mu\text{g}/\text{mL}$; this is markedly reduced by

increasing concentrations (i.e., doses) of fentanyl or alfentanil. The propofol Cp_{50} for skin incision when combined with benzodiazepine premedication (lorazepam, 1 to 2 mg) and 66% nitrous oxide is 2.5 $\mu\text{g}/\text{mL}$ (venous).⁹¹ This concentration is reduced to 1.7 $\mu\text{g}/\text{mL}$ when morphine (0.15 mg/kg) rather than lorazepam is used for premedication. The concentration of propofol (when combined with 66% nitrous oxide) required during minor surgery is 1.5 to 4.5 $\mu\text{g}/\text{mL}$, and the concentration for major surgery is 2.5 to 6 $\mu\text{g}/\text{mL}$.⁹² Awakening usually occurs at concentrations less than 1.6 $\mu\text{g}/\text{mL}$ and orientation occurs at concentrations less than 1.2 $\mu\text{g}/\text{mL}$ when the propofol concentration is decreasing. Not surprisingly, awakening is postponed in the presence of high blood concentrations of opioids. Optimal propofol blood concentrations have been defined when combined with several opioids including remifentanil, alfentanil, sufentanil, and fentanyl that assure adequate anesthesia and the most rapid return to consciousness, postoperatively (Table 23.2). In the presence of remifentanil, a relatively large-dose opioid anesthetic is recommended. Yet, with fentanyl an accompanying large dose of propofol should be used to assure rapid return to recovery postoperatively (Fig. 23.4). When equilibration between blood and effect site is allowed, however, awakening concentrations (2.2 $\mu\text{g}/\text{mL}$) are similar to concentrations associated with loss of verbal command.⁹³

EFFECTS ON THE RESPIRATORY SYSTEM

Apnea occurs after administration of an induction dose of propofol; the incidence and duration of apnea depend on dose, speed of injection, and concomitant premedication.⁹⁴ An induction dose of propofol results in a 25% to 30% incidence of apnea from the respiratory depressant effects of propofol and yet a normal partial pressure of carbon dioxide in the blood (PaCO_2) at induction in the absence of surgical stimulation. Metabolic depression further prevents the PaCO_2 to increase. Yet, the duration of apnea occurring with propofol may be prolonged to more than 30 seconds. The incidence of prolonged apnea (>30 seconds) is increased further by addition of an opiate, either as premedication or just before induction of anesthesia.^{92,95} A maintenance infusion of propofol (100 $\mu\text{g}/\text{kg}/\text{min}$) results in a 40% decrease in tidal volume and a 20% increase in respiratory frequency, with an unpredictable change in minute ventilation. Doubling the infusion rate from 100 to 200 $\mu\text{g}/\text{kg}/\text{min}$ causes a further moderate decrease in tidal volume but no change in respiratory frequency.⁹⁶ As with other hypnotic drugs, spontaneous ventilation is the result of the respiratory depressant effects of the hypnotic agents and the decrease in CO_2 production resulting from the metabolic depression versus the stimulatory effects of the increasing PaCO_2 resulting from apnea and the level of nociception. Propofol (50-120 $\mu\text{g}/\text{kg}/\text{min}$) also depresses the ventilatory response to hypoxia, presumably by a direct action on carotid body chemoreceptors.⁹⁷ Propofol induces bronchodilation in patients with chronic obstructive pulmonary disease. Propofol attenuates vagal (at low concentrations) and methacholine-induced (at high concentrations) bronchoconstriction and seems to have a direct action on muscarinic receptors. Propofol inhibits the receptor-coupled signal transduction pathway through inositol phosphate

TABLE 23.2 Infusion Schemes of Propofol and the Opioids Required to Maintain Effect-Site Concentrations of These Agents*

Opioid	Alfentanil EC ₅₀ -EC ₉₅ (90-130 ng/mL)	Fentanyl EC ₅₀ -EC ₉₅ (1.1-1.6 ng/mL)	Sufentanil EC ₅₀ -EC ₉₅ (0.14-0.20 ng/mL)	Remifentanil EC ₅₀ -EC ₉₅ (4.7-8.0 ng/mL)
Bolus	25-35 µg/kg in 30 sec	3 µg/kg in 30 sec	0.15-0.25 µg/kg in 30 sec	1.5-2 µg/kg in 30 sec
Infusion 1	50-75 µg/kg/h for 30 min	1.5-2.5 µg/kg/h for 30 min	0.15-0.22 µg/kg thereafter	13-22 µg/kg/h for 20 min
Infusion 2	30-42.5 µg/kg/h thereafter	1.3-2 µg/kg/h up to 150 min		11.5-19 µg/kg/h thereafter
Infusion 3		0.7-1.4 µg/kg/h thereafter		
Propofol	Propofol EC ₅₀ -EC ₉₅ (3.2-4.4 µg/mL)	Propofol EC ₅₀ -EC ₉₅ (3.4-5.4 µg/mL)	Propofol EC ₅₀ -EC ₉₅ (3.3-4.5 µg/mL)	Propofol EC ₅₀ -EC ₉₅ (2.5-2.8 µg/mL)
Bolus	2.0-2.8 mg/kg in 30 s	2.0-3.0 mg/kg in 30 s	2.0-2.8 mg/kg in 30 s	1.5 mg/kg in 30 s
Infusion 1	9-12 mg/kg/h for 40 min	9-15 mg/kg/h for 40 min	9-12 mg/kg/h for 40 min	7-8 mg/kg/h for 40 min
Infusion 2	7-10 mg/kg/h for 150 min	7-12 mg/kg/h for 150 min	7-10 mg/kg/h for 150 min	6-6.5 mg/kg/h for 150 min
Infusion 3	6.5-8 mg/kg/h thereafter	6.5-11 mg/kg/h thereafter	6.5-8 mg/kg/h thereafter	5-6 mg/kg/h thereafter

These optimal infusion schemes have been derived from data in female patients undergoing lower abdominal surgery. These should be used as guidelines and be adjusted to the individual needs of the patient.

Reproduced from Vuyk J, Mertens MJ, Olofsen E, et al. Propofol anesthesia and rational opioid selection: determination of optimal EC₅₀-EC₉₅ propofol-opioid concentrations that assure adequate anesthesia and a rapid return of consciousness. *Anesthesiology*. 1997;87:1549-1562, with permission from Lippincott Williams and Wilkins©, 1997; and Kataria BK, Ved SA, Nicodemus HF, et al. The pharmacokinetics of propofol in children using 3 different data-analysis approaches. *Anesthesiology*. 1994;80:104-122.

*When given in combination, within $\pm 15\%$ of the effect-site concentrations that are associated with a 50% and 95% probability of no response to surgical stimuli and the most rapid possible return of consciousness after termination of the infusions.

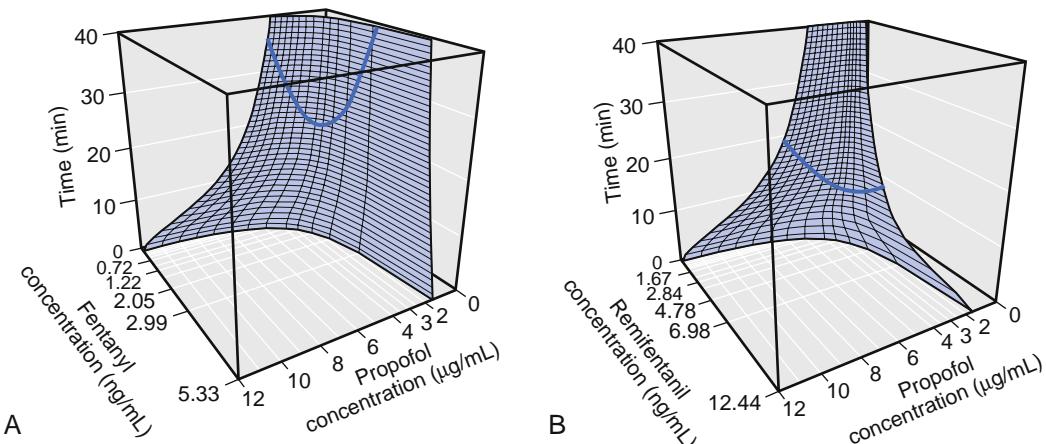


Fig. 23.4 Computer simulation of effect-site propofol and fentanyl (A) or remifentanil (B) concentrations vs. time during the first 40 min after termination of target-controlled infusions of propofol and fentanyl or remifentanil that had been maintained for 300 min at constant target blood or plasma concentration combinations associated with a 50% probability of no response to surgical stimuli. These concentration combinations are represented by the curved line on the bottom of the figure in the x-y plane. The decrease in concentrations following the intraoperative propofol-fentanyl and propofol-remifentanil combinations is represented by the curves running upward from the x-y plane. The curved lines in parallel to the x-y plane represent consecutive 1-min time intervals. The bold lines within the two figures represent the propofol-fentanyl-time and propofol-remifentanil-time relationships at which consciousness is regained in 50% of the patients. (Reproduced from Vuyk J, Mertens MJ, Olofsen E, et al. Propofol anesthesia and rational opioid selection: determination of optimal EC₅₀-EC₉₅ propofol-opioid concentrations that assure adequate anesthesia and a rapid return of consciousness. *Anesthesiology*. 1997;87:1549-1562, with permission from Lippincott Williams and Wilkins©, 1997.)

generation and inhibition of Ca^{2+} mobilization. The preservative used with propofol is important regarding its bronchodilator activity. Propofol with metabisulfite (compared with propofol without metabisulfite) does not inhibit vagal or methacholine-induced bronchoconstriction. Propofol potentiates hypoxic pulmonary vasoconstriction, an effect caused by inhibition of K^{+} (ATP)-mediated pulmonary vasodilatation. Propofol has an impact on the pulmonary pathophysiology of adult respiratory distress syndrome. In an animal model of septic endotoxemia, propofol (10 mg/kg/h) significantly reduced free radical mediated and

cyclooxygenase catalyzed lipid peroxidation. In addition, PaO_2 and hemodynamics were maintained closer to baseline. These benefits of propofol have not yet been confirmed in humans.

EFFECTS ON THE CARDIOVASCULAR SYSTEM

The cardiovascular effects of propofol for induction and maintenance of anesthesia have been evaluated (Table 23.3).⁹⁸ The most prominent effect of propofol is a decrease in arterial blood pressure during induction of

TABLE 23.3 Hemodynamic Changes % After Induction of Anesthesia With Nonbarbiturate Hypnotics

	Diazepam	Droperidol	Etomide*	Ketamine	Lorazepam	Midazolam	Propofol
HR	-9 ± 13	Unchanged	-5 ± 10	0-59	Unchanged	-14 ± 12	-10 ± 10
MBP	0-19	0-10	0-17	0 ± 40	-7 to 20	-12 to 26	-10 to 40
SVR	-22 ± 13	-5 to 15	-10 ± 14	0 ± 33	-10 to 35	0-20	-15 to 25
PAP	0-10	Unchanged	-9 ± 8	+44 ± 47	—	Unchanged	0-10
PVR	0-19	Unchanged	-18 ± 6	0 ± 33	Unchanged	Unchanged	0-10
PAO	Unchanged	+25 ± 50	Unchanged	Unchanged	—	0-25	Unchanged
RAP	Unchanged	Unchanged	Unchanged	+15 ± 33	Unchanged	Unchanged	0-10
CI	Unchanged	Unchanged	-20 ± 14	0 ± 42	0 ± 16	0-25	-10 to 30
SV	0-8	0-10	0-20	0-21	Unchanged	0-18	-10 to 25
LVSWI	0-36	Unchanged	0-33	0 ± 27	—	-28 to 42	-10 to 20
dP/dt	Unchanged	—	0-18	Unchanged	—	0-12	Decreased

*The larger deviations are in patients with valvular disease.

CI, Cardiac index; dP/dt, first derivative of pressure measured over time; HR, heart rate; LVSWI, left ventricular stroke work index; MBP, mean blood pressure; PAO, pulmonary artery occluded pressure; PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SV, stroke volume; SVR, systemic vascular resistance.

From Reves JG, Glass P, Lubarsky DA, et al. Intravenous anesthetics. In: Miller RD, Eriksson LI, Fleischer LA, et al, eds. *Miller's Anesthesia*, 7th ed. Philadelphia: Churchill Livingstone; 2010: 719-768.

anesthesia.^{98a} Independent of the presence of cardiovascular disease, an induction dose of 2 to 2.5 mg/kg produces a 25% to 40% reduction of systolic blood pressure. Similar changes are seen in mean and diastolic blood pressure. The decrease in arterial blood pressure is associated with a decrease in cardiac output/cardiac index (±15%), stroke volume index (±20%), and systemic vascular resistance (15%-25%). Left ventricular stroke work index also is decreased (±30%). When looking specifically at right ventricular function, propofol produces a marked reduction in the slope of the right ventricular end-systolic pressure-volume relationship.

In patients with valvular heart disease, pulmonary artery and pulmonary capillary wedge pressure also are reduced, a finding that implies the resultant decrease in pressure is due to a decrease in preload and afterload. Although the decrease in systemic pressure after an induction dose of propofol is due to vasodilation, the direct myocardial depressant effects of propofol are more controversial. The decrease in cardiac output after propofol administration may be via its action on sympathetic drive to the heart. The hemodynamic response to propofol lags significantly behind that of the hypnotic effect. The effect-site equilibration half-life of propofol is in the order of 2 to 3 minutes for the hypnotic effect and about 7 minutes for the hemodynamic depressant effect.³⁶ This implies that hemodynamic depression increases in a few minutes after a patient has lost consciousness from an induction of anesthesia.

High concentrations of propofol abolish the inotropic effect of α- but not β-adrenoreceptor stimulation and enhance the lusitropic (relaxation) effect of β stimulation. Clinically, the myocardial depressant effect and the vasodilation are dose-dependent and plasma concentration-dependent.⁹⁹ Propofol is a vasodilator due to a reduction in sympathetic activity. The mechanism of this activity is a combination of a direct effect on intracellular smooth muscle calcium mobilization, inhibition of prostacyclin synthesis in endothelial cells, reduction in angiotensin

II-elicited calcium entry,^{100,101} activation of K adenosine triphosphate channels, and stimulation of nitric oxide. The stimulation of nitric oxide may be modulated by any intralipid rather than propofol itself.

Heart rate does not change significantly after an induction dose of propofol. Propofol either may reset or may inhibit the baroreflex, reducing the tachycardic response to hypotension. Propofol also decreases cardiac parasympathetic tone in a dose-dependent manner. Propofol has a minimal direct effect on sinoatrial node function or on normal atrioventricular and accessory pathway conduction. Propofol attenuates the heart rate response to atropine in a dose-dependent manner. Propofol suppresses atrial (supraventricular) tachycardias and probably should be avoided during electrophysiologic studies. The peak plasma concentrations obtained after a bolus dose are substantially higher than the concentrations seen with a continuous infusion and may reach concentrations up to 80 to 100 µg/mL. Because the vasodilatory and myocardial depressant effects are concentration-dependent, the decrease in arterial blood pressure from propofol during the infusion phase (maintenance of anesthesia) is much less than that seen after induction of anesthesia by an intravenous bolus administration of propofol. An infusion of propofol reduces myocardial blood flow and oxygen consumption. Thus, global myocardial oxygen supply-to-demand ratio is likely preserved. The cardioprotective effect of propofol versus volatile anesthetics in patients having cardiac surgery on- or off-cardiopulmonary bypass is less debatable. In two large studies comparing propofol with sevoflurane in patients undergoing cardiac surgery, postoperative troponin levels were lower and hemodynamic function better in patients receiving sevoflurane. A study comparing desflurane with propofol in patients undergoing off-pump coronary artery bypass showed similar results. In contrast, administration of a large-dose of propofol (120 µg/kg/min) or small-dose of propofol (60 µg/kg/min) during cardiopulmonary bypass, or titrating isoflurane throughout surgery,

showed improved troponin levels and better hemodynamic function in the large-dose propofol group compared to the isoflurane or small-dose propofol group. This study suggests that cardio protection with propofol is dose-dependent.¹⁰² Lastly, combinations of propofol with inhaled anesthetics may offer an optimal pre- and postconditioning strategy in patients scheduled for coronary bypass surgery. Isoflurane preconditioning combined with propofol postconditioning acts synergistically in attenuating postischemic myocardial reperfusion injury as determined by surrogate markers of myocardial injury and function.¹⁰³ Heart rate changes are variable when anesthesia is maintained with propofol. The extent of hypotension, the ability for the patient to compensate, and the use of any other concomitant drugs are likely the most important factors in determining what happens to the heart rate after propofol administration.

OTHER EFFECTS

Propofol, similar to thiopental, does not enhance neuromuscular blockade produced by neuromuscular blocking drugs. Propofol produces no effect on the evoked electromyogram or twitch tension; however, good or acceptable tracheal intubating conditions after propofol alone have been reported. Propofol does not trigger malignant hyperthermia and is an appropriate choice in patients with this condition.¹⁰⁴⁻¹⁰⁶ Propofol after a single dose or a prolonged infusion does not affect corticosteroid synthesis or alter the normal response to adrenocorticotrophic hormone (ACTH) stimulation. Propofol in the emulsion formulation does not alter hepatic, hematologic, or fibrinolytic function. Lipid emulsion per se reduces in vitro platelet aggregation, however. Anaphylactoid reactions to the present formulation of propofol have been reported. In at least some patients, the immune response was entirely due to propofol and not to the lipid emulsion. Most patients developing the anaphylactoid response to propofol had a previous history of allergic responses. Perhaps propofol should not be used in patients with multiple drug allergies.¹⁰⁷⁻¹⁰⁹ Propofol alone in intralipid does not trigger histamine release. Fospropofol is metabolized to propofol and formate. Formate concentrations do not increase after fospropofol administration. Propofol also possesses significant antiemetic activity with small (subhypnotic) doses (i.e., 10 mg in adults). The median concentration of propofol with an antiemetic effect was 343 ng/mL, which also causes a mild sedative effect.¹¹⁰ This concentration can be achieved by an initial dose of propofol infusion of 10 to 20 mg followed by 10 µg/kg/min. Propofol used as a maintenance anesthetic during breast surgery was more effective than 4 mg of ondansetron given as prophylaxis in preventing postoperative nausea and vomiting (PONV) (also see Chapter 80). Propofol as an infusion of 1 mg/kg/h (17 µg/kg/min) also has provided excellent antiemetic action after anticancer chemotherapy. At subhypnotic doses, propofol relieves cholestatic pruritus and is likely as effective as naloxone in treating pruritus induced by spinal opiates.

Propofol decreases polymorphonuclear leukocyte chemotaxis, but not adherence phagocytosis and killing. This action contrasts with the effect of thiopental, which inhibits all these chemotactic responses. However, propofol inhibits phagocytosis and killing of *Staphylococcus aureus* and *Escherichia coli*. There have been life-threatening systemic

BOX 23.1 Uses and Doses of Intravenous Propofol

Induction of general anesthesia	1-2.5 mg/kg IV, dose reduced with increasing age
Maintenance of general anesthesia	50-150 µg/kg/min IV combined with N ₂ O or an opiate
Sedation	25-75 µg/kg/min IV
Antiemetic action	10-20 mg IV, can repeat every 5-10 min or start infusion of 10 µg/kg/min

IV, Intravenously; N₂O, nitrous oxide.

From Reeves JG, Glass P, Lubarsky DA, et al. Intravenous anesthetics. In Miller RD, Eriksson LI, Fleischer LA, et al, eds. *Miller's Anesthesia*, 7th ed. Philadelphia: Churchill Livingstone; 2010: 719-768.

infections associated with the use of propofol.¹¹¹ In hospitals where these infections occurred, opened vials and syringes of propofol had positive cultures. The intralipid that acts as the solvent for propofol is an excellent culture medium. Disodium edetate or metabisulfite has been added to the formulation of propofol in an attempt to retard such bacterial growth. Strict aseptic technique still must be observed. The administration of propofol is associated with the development of pancreatitis,¹¹² which may be related to hypertriglyceridemia. Patients who developed hypertriglyceridemia tended to be older, had a longer ICU stay, and received propofol for a longer duration. If propofol is being used for prolonged sedation or at higher infusion rates (especially in elderly patients), serum triglyceride concentrations should be routinely monitored.

Uses

INDUCTION AND MAINTENANCE OF ANESTHESIA

Propofol is suitable for the induction and maintenance of anesthesia (Box 23.1). The intravenous induction dose is 1 to 2.5 mg/kg. Physiologic characteristics that best determine the appropriate dose to induce anesthesia are age, lean body mass, and central blood volume.¹¹³ Propofol may be titrated on the basis of the BIS value for maintenance of anesthesia and to assure adequacy of anesthesia and prevention of overdosing. Premedication with an opiate or a benzodiazepine, or both, markedly reduces the necessary induction dose.¹¹⁴⁻¹¹⁶ The induction dose needs to be reduced in elderly patients and a dose of 1 mg/kg (with premedication) to 1.75 mg/kg (without premedication) is recommended for inducing anesthesia in patients older than 60. Furthermore, older and sicker (ASA class III to IV) patients develop more profound hypotension, especially when propofol is combined with an opiate (also see Chapter 65). To prevent hypotension in sicker patients or in patients presenting for cardiac surgery, intravenously administered fluids should be given as tolerated, and propofol titrated to achieve the desired anesthetic state. In general, for both pharmacokinetic and pharmacodynamic reasons elderly patients (>80 years old) require half the dose of young patients (<20 years)¹¹⁷. For induction in children, the ED₉₅ (2-3 mg/kg) is increased, primarily because of pharmacokinetic differences. Children demonstrate a smaller

central compartment, an increased metabolic clearance, and larger volumes of distribution of propofol relative to adult patients.⁶⁹ Propofol, when used for induction of anesthesia in short-lasting procedures, results in a significantly quicker recovery and an earlier return of psychomotor function compared with thiopental or methohexitol, regardless of the anesthetic used for maintenance of anesthesia.

Several infusion schemes have been used to achieve adequate plasma concentrations of propofol. After an induction dose, an infusion of 100 to 200 $\mu\text{g}/\text{kg}/\text{min}$ is usually needed. The infusion rate is titrated to individual requirements and the surgical stimulus. When combined with propofol, the required infusion rate and concentration of opiates, midazolam, clonidine, or ketamine should be reduced.^{20,118} Because opioids alter the concentration of propofol required for adequate anesthesia, the time to awakening and recovery can be influenced by these drug combinations. Also, opioids affect both the pharmacokinetics and the pharmacodynamics of propofol. Alfentanil decreases the elimination clearance of propofol from 2.1 L/min to 1.9 L/min, the distribution clearance from 2.7 L/min to 2.0 L/min, and the peripheral volume of distribution from 179 L to 141 L. The pharmacokinetic parameters of propofol are affected by cardiac output, heart rate, and plasma alfentanil concentration.³⁹ Similarly, midazolam reduces propofol's metabolic clearance from 1.94 to 1.61 L/min, Cl_2 from 2.86 to 1.52 L/min, and Cl_3 from 0.95 to 0.73 L/min. Consequently, in the presence of both midazolam and alfentanil propofol concentrations become elevated by 20% to 30%.⁵³ The infusion rate required to achieve the combination with the shortest recovery is propofol, 1 to 1.5 mg/kg followed by 140 $\mu\text{g}/\text{kg}/\text{min}$ for 10 minutes followed by 100 $\mu\text{g}/\text{kg}/\text{min}$, and alfentanil, 30 $\mu\text{g}/\text{kg}$ followed by an infusion of 0.25 $\mu\text{g}/\text{kg}/\text{min}$, or fentanyl, 3 $\mu\text{g}/\text{kg}$ followed by 0.02 $\mu\text{g}/\text{kg}/\text{min}$.

As indicated previously, increasing age is associated with a decrease in propofol infusion requirements, whereas these requirements are larger in children and infants. The blood levels of propofol alone for loss of consciousness are 2.5 to 4.5 $\mu\text{g}/\text{mL}$, and the blood concentrations (when combined with nitrous oxide) required for surgery are 2.5 to 8 $\mu\text{g}/\text{mL}$. Similar concentrations are necessary when propofol is combined with an opioid for a total IV technique. The knowledge of these levels and of the pharmacokinetics of propofol has enabled the use of pharmacokinetic model–driven infusion systems to deliver propofol as a continuous infusion for the maintenance of anesthesia. A meta-analysis of recovery data after either propofol for maintenance or the newer volatile anesthetics indicated only minor differences in times to reach recovery goals; however, the incidence of nausea and vomiting remained significantly less frequent in the patients given propofol for maintenance of anesthesia.

Propofol can be used as a maintenance of anesthesia infusion regimen for cardiac surgery. Using reduced and titrated doses of propofol for induction of anesthesia and titrated infusion rates of 50 to 200 $\mu\text{g}/\text{kg}/\text{min}$ combined with an opioid for maintenance, propofol provides intraoperative hemodynamic control and ischemic episodes similar to those with either enflurane/opioid or a primary opioid technique.

Blood propofol concentrations increase in the presence of hemorrhagic shock. Shock affects the pharmacokinetics and pharmacodynamics of propofol. Shock results in slower intercompartmental clearances and shock shifts the

concentration effect relationship to the left, demonstrating a 2.7-fold decrease in the effect-site concentration required to achieve 50% of the maximal effect in the BIS.¹¹⁹ These pharmacokinetic changes may be reversed with intravenous fluid resuscitation. The propofol doses needed to reach a 50% decrease from baseline BIS, and no movement after noxious stimuli, are reduced by hemorrhagic shock by 54% and 38%, respectively. Hemorrhagic shock decreases the effect-site concentration that produced 50% of the maximal BIS effect from 11.6 ± 3.8 to $9.1 \pm 1.7 \mu\text{g}/\text{mL}$ and that producing a 50% probability of movement from 26.8 ± 1.0 to $20.6 \pm 1.0 \mu\text{g}/\text{mL}$.¹²⁰

SEDATION

Propofol has been evaluated for sedation during surgical procedures and for patients receiving mechanical ventilation in the ICU.^{120a} As noted earlier, tolerance can occur with propofol. Increased propofol requirement occurs with repeated anesthetic administration in a limited time period in individual patients and an increased infusion requirement when propofol is infused for prolonged periods.⁷⁴ Infusion rates required for sedation to supplement regional anesthesia in healthy patients are half or less than the rates required for general anesthesia (i.e., 30–60 $\mu\text{g}/\text{kg}/\text{min}$). In elderly patients (>65 years old) and in sicker patients, the infusion rates that are necessary are markedly reduced up to 50% compared to 20-year-old patients. The infusion should be individually titrated to the desired effect. The pharmacokinetic profile of propofol makes it a suitable choice for long-term (days) sedation. This should always be weighed, though, against the hemodynamic side effects, tolerance, and rare occurrences of hypertriglyceridemia (and potential pancreatitis) or propofol infusion syndrome. Maintaining the smallest possible dose required for the desired level of sedation with potential “sedation holidays” should be considered as part of a long-term propofol sedation regimen. In addition, the FDA has specifically recommended against the use of propofol for the prolonged sedation of pediatric patients. The sedation guidelines of the American College of Critical Care Medicine also recommend “that patients receiving propofol for long-term sedation should be monitored for unexplained metabolic acidosis or arrhythmias. Drugs other than propofol should be considered for patients with escalating vasopressor or inotrope requirements or cardiac failure during large-dose propofol infusions.” The recommended maximal dose of propofol infusion rate is 80 $\mu\text{g}/\text{kg}/\text{min}$ (<5 mg/kg/h).¹²¹ Generally, at propofol infusion rates more rapid than 30 $\mu\text{g}/\text{kg}/\text{min}$, patients are amnesic.

SIDE EFFECTS AND CONTRAINDICATIONS

In December 2016 the FDA issued a warning raising concerns about the potential risks to fetal brain development with general anesthetics, including propofol. Animal studies show that prolonged or repetitive propofol exposure to the developing fetal brain may be related to propofol neurotoxicity. Minimizing fetal exposure to propofol and other general anesthetics is therefore important and advisable.^{121a,121b}

Next to its hypnotic effects, accumulating evidence suggests that propofol may affect cancer development

through direct and indirect manners. Propofol exerts anti-tumor potential partly due to regulation of the expression and transfer of miRNAs. In addition, propofol impacts the degree of immunosuppression by modulating immune cells and cytokines. This results in reduced cancer cell mobility in some cancers and increased apoptosis of cancer cells in others. The clinical impact of the cancer-modulating effects of propofol needs further investigation.^{121c} Induction of anesthesia with propofol is often associated with pain on injection, myoclonus, apnea, hypotension, and, rarely, thrombophlebitis of the vein into which propofol is injected.¹²² Pain on injection is reduced by using a large vein, avoiding veins in the dorsum of the hand, and adding lidocaine to the propofol solution or changing the propofol formulation. Multiple other drugs and distraction techniques have been investigated to reduce the pain on injection of propofol. Pretreatment with a small dose of propofol, opiates, nonsteroidal anti-inflammatory drugs, ketamine, esmolol/metoprolol, magnesium, a flash of light, clonidine/ephedrine combination, dexamethasone, and metoclopramide all have been tested with variable efficacy.

Propofol infusion syndrome is a rare but lethal syndrome associated with infusion of propofol at 4 mg/kg/h or more for 48 hours or longer.¹²³ Yet, cases have been reported with smaller dosage schemes given for only 3 hours.¹²⁴ It was first described in children, but subsequently has been observed in critically ill adults.^{125,126} The clinical features of propofol infusion syndrome are acute refractory bradycardia leading to asystole, in the presence of one or more of the following: metabolic acidosis (base deficit >10 mmol/L⁻¹), rhabdomyolysis, hyperlipidemia, and enlarged or fatty liver. Other features include cardiomyopathy with acute cardiac failure, skeletal myopathy, hyperkalemia, hepatomegaly, and lipemia. The symptoms and signs are the result of muscle injury and of the release of intracellular toxic contents. The major risk factors for its development are poor oxygen delivery, sepsis, serious cerebral injury, and large propofol dosage. Predisposing factors for the propofol infusion syndrome are likely genetic disorders impairing fatty acid metabolism, such as medium-chain acyl CoA (MCAD) deficiency and low carbohydrate supply. Because lipemia has been noted, a failure of hepatic lipid regulation, possibly related to poor oxygenation or a lack of glucose, may be the cause. In some cases, an increasing lipemia was the first indication of impending propofol infusion syndrome onset, so lipemia is a sign.

Barbiturates

HISTORY

Barbiturates were discovered in the early twentieth century. The first barbiturate to cause loss of consciousness within one arm-brain circulation time was hexobarbital. After the clinical introduction of thiopental by Waters and Lundy in 1934, thiopental became preferred clinically because of its rapid onset of action and short duration, without the excitatory effects of hexobarbital.¹²⁷ Although criticized after many casualties during the attack on Pearl Harbor as “the cause of more fatal casualties among the servicemen at Pearl Harbor than were the enemy bombs,”

the barbiturates continued to be widely used in clinical practice.¹²⁸ Many other barbiturate derivatives have been synthesized throughout the past decades, yet none have enjoyed the clinical success and popularity of thiopental.

Physicochemical Characteristics

CHEMISTRY AND FORMULATION

Barbiturates are hypnotically active drugs that are derivatives of barbituric acid (2,4,6-trioxohexahydropyrimidine), a hypnotically inactive pyrimidine nucleus that is formed by the condensation of malonic acid and urea (Fig. 23.5). The two major classes of barbiturates are the oxybarbiturates and thiobarbiturates with either an oxygen at position 2 or with a sulfur in position 2, respectively. Through keto-enol tautomerization, the oxygen or sulfur in position 2 becomes a reactive species in the enol form. This allows for the formation of water-soluble barbiturate salts in alkaline solutions and permits the IV use of barbiturates. Although tautomerization to the enol form allows for the creation of salts, the substitution of the hydrogen attached to the carbon atom in position 5 with aryl or alkyl groups gives the barbiturates their hypnotic activity. Only thiopental and thiamylal, thiobarbiturates, and methohexit, an oxybarbiturate, have been used for induction of anesthesia (Fig. 23.6). The formulation of barbiturates involves preparation as sodium

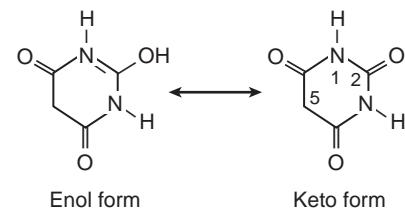


Fig. 23.5 The keto and enol tautomeric forms of barbituric acid with the sites of substitution in the hypnotically active barbiturates identified as 1, 2, and 5.

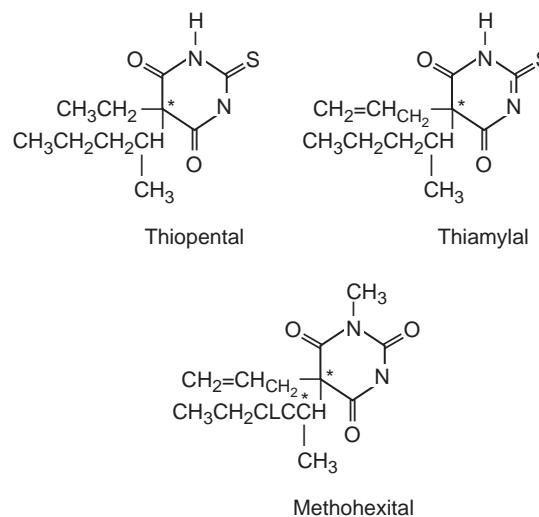


Fig. 23.6 Hypnotically active barbiturates commonly used for induction, with their asymmetric centers indicated by an asterisk.

salts (mixed with 6% by weight anhydrous sodium carbonate) and then reconstitution with either water, glucose 5%, or normal saline to produce a 2.5% solution of thiopental, a 2% solution of thiamylal, or a 1% solution of methohexital. The thiobarbiturates are stable for 1 week if refrigerated after reconstitution, and methohexital remains available for use for 6 weeks after reconstitution. Barbiturates cannot be reconstituted with lactated Ringer solution or mixed with other acidic solutions, as a decrease in the alkalinity of the solution can result in precipitation of the barbiturates as free acids. Examples of drugs that are not to be coadministered or mixed in solution with the barbiturates are atracurium, vecuronium, rocuronium, suxamethonium, alfentanil, sufentanil, dobutamine, dopamine, esketamine, and midazolam. Mixing of thiopental with vecuronium or pancuronium results in the formation of precipitate that may occlude the IV line during a rapid sequence induction of anesthesia.¹²⁹

Structure-Activity Relationships

As noted earlier, substitutions at the 5, 2, and 1 positions confer different pharmacologic activities to the barbiturate nucleus. Substitutions at position 5 with either aryl or alkyl groups produce hypnotic and sedative effects, whereas substitution at C5 with a phenyl group produces anticonvulsant activity. An increase in length of one or both side chains of an alkyl group at C5 increases hypnotic potency. Barbiturates used in clinical practice have either an oxygen or sulfur at C2. Substitution of a sulfur at position 2 produces a more rapid onset of action, as with thiopental. The addition of a methyl or ethyl group at position 1 also may produce a more rapid onset of action, as with methohexital. However, excitatory side effects, including tremor, hypertonus, and involuntary movement, may occur upon administration.

Pharmacokinetics

METABOLISM

The barbiturates (with the exception of phenobarbital) are metabolized hepatically. The metabolites are almost all inactive, water-soluble, and excreted in the urine. Barbiturates are biotransformed by four processes: (1) oxidation of the aryl, alkyl, or phenyl moiety at C5; (2) N-dealkylation; (3) desulfuration of the thiobarbiturates at C2; and (4) destruction of the barbituric acid ring.¹³⁰ Oxidation is the most important pathway, producing polar (charged) alcohols, ketones, phenols, or carboxylic acids. These metabolites are readily excreted in the urine or as glucuronic acid conjugates in the bile. Hydrolytic cleavage of the barbituric acid ring forms a minimal contribution to the total metabolism of barbiturates, since the ring is stable in vivo. Drugs that induce oxidative microsomes or long-term administration enhance the metabolism of barbiturates. The hepatic enzyme induction by barbiturates is the reason that they are not recommended for administration to patients with acute intermittent porphyria. Barbiturates may precipitate an attack by stimulating γ -aminolevulinic acid synthetase, the enzyme responsible for the production of porphyrins.¹³¹

As mentioned earlier, hepatic metabolism accounts for the elimination of all of the barbiturates with the exception of phenobarbital. Renal excretion accounts for 60% to 90% of phenobarbital excretion in an unchanged form. The alkalinization of urine with bicarbonate enhances the renal excretion of phenobarbital. Other barbiturates are excreted unchanged by the kidney only in trivial amounts.

Methohexital is metabolized in the liver by oxidation to an alcohol and N-dealkylation. Methohexital exhibits similar distribution half-lives, volumes of distribution, and protein bindings as thiopental. A marked difference exists, however, in plasma disappearance and elimination half-lives (4 hours for methohexital and 12 hours for thiopental). This difference is due to the threefold more rapid rate of hepatic clearance of methohexital (mean 7.8-12.5 mL/kg/min).¹³² The hepatic extraction ratio of methohexital (clearance to hepatic blood flow) is approximately 0.5, indicating that the liver extracts 50% of the drug presented to it. This ratio differs from the smaller hepatic extraction ratio of thiopental (0.15).

Barbiturate pharmacokinetics have been described in physiologic and compartmental models.¹³³ Both of these pharmacokinetic models describe rapid redistribution as the primary mechanism that terminates the action of a single induction dose. Physiologic models of barbiturates describe a rapid mixing of the drug within the central blood volume followed by a quick distribution of the drug to highly perfused, low-volume tissues (i.e., brain) with a slower redistribution of the drug to lean tissue (muscle), which terminates the effect of the initial (induction of anesthesia) dose. In these models, adipose tissue uptake and metabolic clearance (elimination) play only a minor role in the termination of the effects of the induction dose. This is a result of the minimal perfusion ratio of adipose tissue compared with other tissues and the slow rate of removal. Compartmental model values for thiopental and methohexital, the most commonly used barbiturates for induction of anesthesia, are given in Table 23.1. The compartmental model explains the delay of recovery when a continuous infusion of a barbiturate is used. This model describes how the termination of effect becomes increasingly dependent on the slower process of uptake into and redistribution from adipose tissue and elimination clearance through hepatic metabolism. After prolonged infusions, the pharmacokinetics of barbiturate metabolism is best approximated by nonlinear Michaelis-Menten metabolism. In usual doses (4-5 mg/kg), thiopental exhibits first-order kinetics (i.e., a constant fraction of drug is cleared from the body per unit time); however, at very high doses of thiopental (300-600 mg/kg) with receptor saturation, zero-order kinetics occur (i.e., a constant amount of drug is cleared per unit time). The volume of distribution is slightly larger in female patients, causing a longer elimination half-life.¹³⁴ Pregnancy also increases the volume of distribution of thiopental, prolonging the elimination half-life.¹³⁵ Even at advanced stages of liver cirrhosis, the clearance of thiopental is not altered. Because of its lipophilicity, relatively large volume of distribution, and low rate of hepatic clearance, thiopental can accumulate in tissues, especially if given in large doses over a prolonged period. The plasma drug level increases when repeated doses of drug are given. Although not used

in routine clinical practice, appropriately designed infusion schemes ensure constant blood levels, maintaining the desired hypnotic effect.

Pharmacology

MECHANISM OF ACTION

The mechanisms of action of barbiturates on the CNS are largely unknown, with the exception of their action on the GABA_A receptor.^{136,137} Perhaps the NMDA receptors are involved with the effects of barbiturates.¹³⁸⁻¹⁴⁰ The effects of barbiturates on the CNS have been grouped into two categories: (1) enhancement of the synaptic actions of *inhibitory* neurotransmitters, and (2) blockade of the synaptic actions of *excitatory* neurotransmitters.¹⁴¹ GABA is the principal inhibitory neurotransmitter in the mammalian CNS, and the GABA_A receptor is the only site proven to be involved in barbiturate-induced anesthesia.¹³⁷ The GABA_A receptor is a chloride ion channel, composed of five subunits, with specific sites of action for GABA, barbiturates, benzodiazepines, and other molecules. The binding sites are at the interface of the specific subunits, where the combination of the adjacent subunits determine the affinity and selectivity for drugs like propofol, etomidate, or pentobarbital. Of each subunit multiple types exist, leading to various compositions of the GABA_A receptor. Progressive insights in the composition of these binding sites may be useful in developing novel clinical anesthetics.^{141a} Barbiturate binding to the GABA_A receptor enhances and mimics the action of GABA by increasing chloride conductance through the ion channel. This causes hyperpolarization of the cell membrane and increases the threshold of excitability of the postsynaptic neuron. At low concentrations barbiturates enhance the effects of GABA, decreasing the rate of dissociation of GABA from its receptor and increasing the duration of GABA-activated chloride ion channel openings. This enhancement of the action of GABA is likely responsible for the sedative-hypnotic effects of the barbiturates. At larger concentrations, the barbiturates activate the chloride channels directly, without the binding of GABA, acting as the agonist itself. The GABA-mimetic effect at slightly higher concentrations may be responsible for what is termed barbiturate anesthesia.¹³⁷

The second mechanism of action of barbiturates involves the inhibition of the synaptic transmission of excitatory neurotransmitters, such as glutamate and acetylcholine. The actions of the barbiturates to block excitatory CNS transmission are specific for synaptic ion channels. Thiopental, however, may exert GABA-independent effects on the glutaminergic-NMDA system. In two studies on effects in the rat prefrontal cortex, thiopental decreased extracellular glutamate levels in the CNS and decreased NMDA-gated currents in a concentration-dependent manner.^{139,140}

Effects on Cerebral Metabolism (Also see Chapter 57)

Barbiturates, like other CNS depressants, have potent effects on cerebral metabolism. A dose-related depression of cerebral metabolic oxygen consumption rate (CMRO₂) progressively slows the EEG, reduces the rate of adenosine triphosphate consumption, and enhances protection

from partial cerebral ischemia. The relationship between depressed metabolism and drug requirement was shown when thiopental was not eliminated (i.e., sustained with an extracorporeal circulation pump).¹⁴² When the EEG became isoelectric, a point at which cerebral metabolic activity is roughly 50% of baseline,¹⁴³ no further decreases in CMRO₂ occurred. These findings support the hypothesis that metabolism and function of the brain are coupled. Barbiturates reduce the metabolic activity concerned with neuronal signaling and impulse traffic, not the metabolic activity corresponding to basal metabolic function. The only way to suppress baseline metabolic activity concerned with cellular activity is via hypothermia.¹⁴³ The effect of barbiturates on cerebral metabolism is maximized at a 50% depression of cerebral function, leaving all metabolic energy for the maintenance of cellular integrity. With the reduction in CMRO₂, there is a parallel reduction in cerebral perfusion, which is seen in decreased cerebral blood flow (CBF) and ICP. With reduced CMRO₂, cerebral vascular resistance increases, and CBF decreases.¹⁴⁴ The ratio of CBF to CMRO₂ remains unchanged. Even though the mean arterial pressure (MAP) decreases, barbiturates do not compromise the overall CPP because the CPP equals MAP minus ICP. In this relationship, ICP decreases more than MAP after barbiturate administration, preserving CPP.

Pharmacodynamics

Sufficient doses of barbiturates cause loss of consciousness, amnesia, and respiratory and cardiovascular depression, known as general anesthesia. The response to pain and other noxious stimulation during general anesthesia seems to be depressed. Pain studies reveal that barbiturates may decrease the pain threshold. This antianalgesic effect occurs only with low blood levels of barbiturates, which might be achieved with small doses of thiopental for induction of anesthesia or after emergence from thiopental. The amnesic effect of barbiturates is less pronounced than that produced by benzodiazepines.

Effects on the Central Nervous System

Drugs with high lipid solubility and a low degree of ionization cross the blood-brain barrier rapidly, producing a fast onset of action.¹³⁷ Most barbiturates exist in a nonionized form. Thiopental and methohexitol are more lipid soluble than pentobarbital, which is clinically reflected by the more rapid onset of action of thiopental and methohexitol compared to pentobarbital.¹⁴⁵ Only the nonionized form of a drug can directly traverse the cellular membranes. Thiopental has a pK_a of 7.6. Approximately 50% of thiopental is nonionized at physiologic pH, which accounts partly for the rapid accumulation of thiopental in the cerebrospinal fluid (CSF) after IV administration.¹⁴⁶ Methohexitol is 75% nonionized at pH 7.4, which may explain the slightly more rapid effect of methohexitol compared to thiopental. As pH decreases, with poor perfusion, barbiturates have a larger fraction of nonionized drug available to cross the blood-brain barrier.¹⁴⁶

The onset of action in the CNS is affected by protein binding, because only unbound drug (free drug) can cross the blood-brain barrier.¹⁴⁷ Barbiturates are highly bound to albumin and other plasma proteins, where the thiobarbiturates are more highly protein bound than are the

oxybarbiturates. The degree of protein binding of a drug is influenced by the physiologic pH and disease states, which alter the absolute amount of protein. Most barbiturates tend to experience peak protein binding at or around pH 7.5. The final factor governing the rapidity of drug penetration of the blood-brain barrier is the plasma drug concentration, causing a concentration gradient. The two primary determinants of the plasma concentration are the *dose* administered and the *rate* (speed) of administration. As the dose of thiopental over the same time is increased, an increased percentage of patients will be anesthetized.¹⁴⁸ Concerning absolute dose, 2 mg/kg produced anesthesia in 20% of patients, whereas a dose of 2.4 mg/kg produced anesthesia in 80% of patients. Similarly, the speed of injection influences the effect of thiopental. A smaller amount of drug is required to produce anesthesia when the dose rate of the administration is over 5 seconds as opposed to over 15 seconds.

Because of the equilibrium between brain concentration and plasma concentration, factors that determine the rate of onset of barbiturate effects also affect their termination. Lipid solubility, degree of ionization, and CSF drug concentration affect the movement of drug from the CSF to plasma. As plasma levels decrease, drug levels in the brain and CSF decrease. The most important factors in the termination of drug effect are those that govern plasma disappearance of the drug. These are generally divided into a rapid redistribution phase and a slow metabolic and second redistribution phase. In a classic pharmacologic study, Brodie and coworkers¹⁴⁹ showed that awakening from thiopental occurred because the plasma concentration rapidly declined. They further showed that the cause of the rapid plasma decay of thiopental was not metabolism of the drug but was rather due to a redistribution of the drug to other tissues throughout the body. The relationship of the plasma drug level and drug redistribution to the onset and termination of effect is illustrated in Fig. 23.7. Clinically, patients awake from a single dose of thiopental 5 to 10 minutes after administration, as the drug is redistributed from highly perfused CNS tissues to well-perfused lean tissues. The termination of effect after multiple drug administrations or constant infusion depends on the elimination of the drug from the blood, which becomes increasingly more dependent on first-order metabolism than redistribution and is a function of its context-sensitive decrement time (see Fig. 23.3). Awakening may be delayed in older patients because of increased CNS sensitivity, alterations in metabolism, or decreased central volume of distribution relative to younger adults.¹⁵⁰ The initial volume of distribution is less in elderly patients than in young patients, which explains a smaller dose requirement for the onset effect. Pediatric patients (<13 years old) seem to have a more rapid rate of total clearance and a shorter rate of plasma thiopental clearance than do adults, which theoretically might result in earlier awakening, especially after multiple doses of the drug.¹⁵¹ There is little difference in distribution of thiopental and methohexitol, which may explain the similar wakeup times. There is, however, a difference in the rate of total body clearance, being more rapid for methohexitol. This disparity explains the difference found in the psychomotor skills of patients and the earlier full recovery after methohexitol. Despite some residual effects, methohexitol is cleared more rapidly

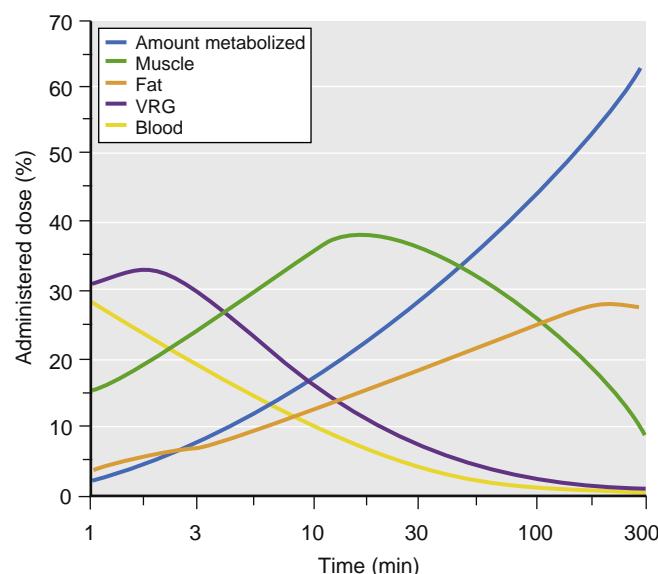


Fig. 23.7 After delivery of an IV bolus, the percentage of thiopental remaining in blood rapidly decreases as drug moves from blood to body tissues. The time to attainment of peak tissue levels is a direct function of tissue capacity for barbiturate relative to blood flow. A larger capacity or smaller blood flow is related to a longer time to a peak tissue level. Initially, most thiopental is taken up by the vessel-rich group (VRG) of tissues because of their high blood flow. Subsequently, drug is redistributed to muscle and to a lesser extent to fat. Throughout this period, small but substantial amounts of thiopental are removed and metabolized by the liver. In contrast to removal by tissues, this removal is cumulative. The rate of metabolism equals the early rate of removal by fat. The sum of this early removal by fat and metabolism is the same as the removal by muscle. (Redrawn from Saidman LJ. Uptake, distribution and elimination of barbiturates. In: Eger EI [ed]. *Anesthetic Uptake and Action*. Baltimore: Williams & Wilkins; 1974.)

than thiopental, which explains why methohexitol is preferred for use by some clinicians when rapid awakening is desirable, such as in outpatient anesthesia. Prolongation of early and late recovery by the barbiturates is the primary reason behind the fact that they have been largely replaced by propofol.

Effects on the Respiratory System

Barbiturates produce dose-related central respiratory depression. The evidence for central depression is a correlation between EEG suppression and diminished minute ventilation. Peak respiratory depression (as measured by the slope of carbon dioxide concentration in the blood) and maximum depression of minute ventilation after delivery of thiopental (3.5 mg/kg) occurs 1 to 1.5 minutes after administration. These variables return to predrug levels rapidly, and within 15 minutes the drug effects are barely detectable.¹⁵² Patients with chronic lung disease are slightly more susceptible to the respiratory depression of thiopental. The ventilatory pattern with thiopental induction has been described as “double apnea,” that is an initial apnea of a few seconds occurring upon drug administration, succeeded by a few breaths of reasonably adequate tidal volume, which is followed by a more prolonged period of apnea, typically of approximately 25 seconds. This apnea occurs in at least 20% of cases. During the induction of anesthesia with thiopental, ventilation must be assisted or controlled to provide adequate respiratory exchange. Like thiopental,

methohexitol is a central respiratory system depressant.¹⁵² Induction doses (1.5 mg/kg) significantly decrease the slope of the ventilatory response to carbon dioxide, with a maximal reduction at 30 seconds after drug administration.¹⁵³ The peak decrease in tidal volume occurs 60 seconds after methohexitol administration. All variables return to baseline within 15 minutes. In contrast to the effects on ventilation, patients awaken within about 5 minutes after the administration of methohexitol (1.5 mg/kg).

Effects on the Cardiovascular System

Cardiovascular depression from barbiturates is a result of central and peripheral (direct vascular and cardiac) effects. The primary cardiovascular effect of a barbiturate during induction of anesthesia is peripheral vasodilation causing a pooling of blood in the venous system. Mechanisms for the decrease in cardiac output include (1) direct negative inotropic action, due to a decrease of calcium influx into the cells, (2) decreased ventricular filling, due to increased capacitance, and (3) transiently decreased sympathetic outflow from the CNS.¹⁵⁴ The increase in heart rate (10% to 36%) that accompanies thiopental administration probably results from the baroreceptor-mediated sympathetic reflex stimulation of the heart in response to the decrease in output and pressure. The cardiac index, as well as the MAP, is unchanged or reduced. Hemodynamic changes are dependent on the infusion rate of thiopental. In the dose ranges hitherto studied, no relationship between plasma thiopental level and hemodynamic effect has been found. There is little difference in the responses after thiopental and methohexitol administration in patients with heart disease. The increase in heart rate (11%–36%) encountered in patients with coronary artery disease anesthetized with thiopental (1–4 mg/kg) is potentially deleterious because of the obligatory increase in myocardial oxygen consumption that accompanies the increased heart rate. In a study in dogs, thiopental prolonged the QT interval, flattened T waves, and increased QT dispersion during and after induction.¹⁵⁰ Thiopental may not be the most appropriate choice for patients with a susceptibility to ventricular dysrhythmias or a prolonged QT interval, such as acidotic patients or conditions that prolong the QT interval, such as long-term dialysis or advanced cirrhosis. Patients who have normal coronary arteries have no difficulty in maintaining adequate coronary blood flow to meet the increased myocardial oxygen consumption.¹⁵⁵ Thiopental should be avoided in hypovolemic patients because there is a significant reduction in cardiac output (69%) and a significant decrease in arterial blood pressure.¹⁵⁶ Patients without adequate compensatory mechanisms may have serious hemodynamic depression with a thiopental induction of anesthesia.

Other Effects

The side effects of injecting barbiturates include a garlic or onion taste (40% of patients), allergic reactions, local tissue irritation, and rarely, tissue necrosis. A transient urticarial rash may develop on the head, neck, and trunk. More severe reactions such as facial edema, hives, bronchospasm, and anaphylaxis can occur. Treatment of anaphylaxis is symptomatic. Thiopental and thiamylal produce fewer excitatory symptoms with induction than methohexitol, which produces cough, hiccups, tremors, and twitching

approximately five times more often. Tissue irritation and local complications may occur more frequently with the use of thiopental and thiamylal than with methohexitol.

The consequences of accidental arterial injection may be severe. The degree of injury is related to the concentration of the drug. Treatment consists of (1) dilution of the drug by the administration of saline into the artery, (2) heparinization to prevent thrombosis, and (3) brachial plexus block. Overall, the proper administration of thiopental intravenously is remarkably free of local toxicity.

Phenobarbital is used experimentally as an inducer of the cytochrome P450 (CYP) system in rodents, in particular of the CYP2B enzymes. In human hepatocyte culture, phenobarbital acts as an inducer of the CYP2B6, CYP2C9, CYP2C19, and CYP3A4 enzymes. This phenomenon may cause changes in the metabolism of drugs that are administered concomitantly.¹⁵⁷ On the other hand, the metabolism of thiopental can be influenced by concomitant drugs like selective serotonin reuptake inhibitors (SSRIs). These drugs are used frequently by patients who are treated by electroconvulsive therapy, in whom an induction with thiopental or thiamylal is performed.¹⁵⁸

Uses

INDUCTION AND MAINTAINANCE OF ANESTHESIA

Barbiturates are used clinically for induction and maintenance of anesthesia and premedication. Methohexitol is the drug of choice for providing anesthesia during electroconvulsive therapy.¹⁵⁹ Other barbiturates used in this field are thiopental and thiamylal. Less frequently, barbiturates are used to provide cerebral protection in patients at risk of developing incomplete ischemia. The three barbiturates that are used most commonly for IV anesthesia induction and maintenance are thiopental, thiamylal, and methohexitol. Thiopental is an excellent drug to use for induction of anesthesia. The prompt onset (15–30 seconds) of action and smooth induction are advantages for this drug. The rapid emergence, particularly after single use for induction, also was a reason for the widespread use of thiopental in this setting. Thiopental can be used to maintain general anesthesia because repeated doses reliably sustain unconsciousness and contribute to amnesia but should not be the drug of first choice as the hypnotic component in balanced anesthesia. A review of the role of anesthetics on the risk of awareness during surgery show that benzodiazepines reduce awareness compared to thiopental, ketamine, and placebo. Wakefulness is reduced by ketamine and etomidate, compared with thiopental. The evidence is not strong due to the risk of bias, the very small event rate, and the heterogeneity in definition of awareness.¹⁶⁰

Methohexitol is the only IV barbiturate used for induction of anesthesia that can compete with thiopental. With a dose of 1 to 2 mg/kg, induction and emergence from anesthesia is rapid. Methohexitol also may be used as a hypnotic component to maintain anesthesia. Similar to thiopental, it is not an analgesic. Additional opioids or volatile anesthetics are required to provide a balanced technique satisfactory for general anesthesia during surgery. Because methohexitol is

TABLE 23.4 Recommended Doses of Barbiturates for Anesthesia Induction and Maintenance

Drug	Induction Dose (mg/kg) ^{*†}	Onset (s)	Intravenous Maintenance Infusion
Thiopental	3-4	10-30	50-100 mg every 10-12 min
Methohexitol	1-1.5	10-30	20-40 mg every 4-7 min

*Adult and pediatric intravenous doses are roughly the same in milligrams per kilogram.

†Methohexitol can be given rectally in pediatric patients as a 20 to 25 mg/kg dose.

From Reeves JG, Glass P, Lubarsky DA, et al. Intravenous anesthetics. In: Miller RD, Eriksson LI, Fleisher LA, et al, eds. *Miller's Anesthesia*, 7th ed. Philadelphia: Churchill Livingstone; 2010: 719-768.

cleared more rapidly than thiopental, it may be preferred to thiopental for the maintenance of anesthesia, as accumulation and saturation of peripheral sites takes longer. For brief infusion (<60 minutes), recovery from a methohexitol infusion titrated to maintain hypnosis (50-150 µg/kg/min) is similar to that provided by propofol. There are probably upper limits of safe infusion doses yet to be defined, but seizures have occurred in neurosurgical patients after large doses of methohexitol (24 mg/kg).¹⁵⁴ Methohexitol may be given rectally and is absorbed rapidly, and can be used as a premedication drug in pediatric patients. The dose recommended for this use is 25 mg/kg rectal instillation (10% solution through a 14F catheter, 7 cm into rectum).¹⁶¹ With this method of administration, sleep onset is rapid: mean peak plasma levels occur within 14 minutes.

Dosing

Dosing for the two most commonly used barbiturates is listed in Table 23.4. The usual doses of thiopental (3-4 mg/kg) and thiamylal (3-4 mg/kg) are about twice the dose of methohexitol (1-2 mg/kg). In dose-response studies, the ED₅₀ for thiopental ranged from 2.2 to 2.7 mg/kg, and the ED₅₀ for methohexitol was 1.1 mg/kg.¹⁴⁷ There is less interpatient variability in the dose response to barbiturates than to benzodiazepines when used for anesthesia induction, but there still is significant variability in the dose of thiopental required to induce anesthesia.¹⁴⁸ Interpatient dose variability is related to the presence of hemorrhagic shock, cardiac output, lean body mass, obesity, gender, and age. Hemorrhagic shock, lean body mass, age, and obesity explain variability of patient response owing to a decrease in the central volume of distribution. Finally, patients who have severe anemia, burns, malnutrition, widespread malignant disease, uremia, ulcerative colitis, or intestinal obstruction also require smaller induction doses of barbiturates.

Contraindications

The following conditions should be considered a contraindication for the use of IV barbiturates: (1) when there is respiratory obstruction or an inadequate airway, thiopental may worsen respiratory depression; (2) severe cardiovascular instability or shock contraindicate its use; (3) status asthmaticus is a condition in which airway control and ventilation may be worsened further by thiopental; (4) porphyria may be precipitated or acute attacks may be accentuated by the administration of thiopental; and (5) without

proper induction equipment (IV instrumentation) and airway equipment (means of artificial ventilation), thiopental should not be administered.

Benzodiazepines

INTRODUCTION

The benzodiazepines have become a category of drugs widely used in anesthesia as anxiolytics, sedatives, and hypnotics. They exert their action through GABA_A receptors, which are the key targets that mediate most of the clinically important effects of IV anesthetics.¹⁶² In the clinical practice of daily anesthesia, midazolam is often used immediately before induction of anesthesia. The other agonists, diazepam, lorazepam, temazepam, and the antagonist flumazenil are sometimes used. Remimazolam, an ultrashort-acting GABA_A receptor agonist, may be a useful new benzodiazepine in future anesthetic practice. Benzodiazepines are widely prescribed, and addiction to these drugs is a worldwide concern. Research is ongoing to elucidate the neural mechanism of the reward-related effects of benzodiazepines. Reynolds and associates conclude in their findings that α_2 - and α_3 -subunit-containing GABA_A receptors are implicated as key mediators of the reward-related effects of benzodiazepines. This finding has important implications for the development of new drugs with less addictive properties.¹⁶³

Surgical treatment of tumors is often the first line for several types of cancer. Several factors influence the metastatic spread of residual cancer cells. Midazolam is widely used during general anesthesia. Research *in vitro* and *in vivo* conclude that midazolam in contrast to dexmedetomidine has antitumorigenic properties in certain types of cancer in suprACLINICAL dosages.^{163a}

Benzodiazepines were discovered in 1954 by Sternbach and in 1959 chlordiazepoxide (Librium) was the first benzodiazepine patented. Diazepam was synthesized in 1963 in a search for a better compound and was used intravenously to induce anesthesia in 1965.¹⁶⁴ Oxazepam (Seresta), a metabolite of diazepam, was synthesized in 1961 by Bell. Lorazepam (Ativan), a 2'chloro-substitution product of oxazepam, was synthesized in 1971 in an attempt to produce a more potent benzodiazepine. The next major achievement was Fryer and Walser's synthesis in 1976 of midazolam (Versed, Dormicum), the first clinically used water-soluble benzodiazepine, produced primarily for use in anesthesia.¹⁶⁵ An ultrashort-acting benzodiazepine, remimazolam, is in its phase III trial and is promising.¹⁶⁶

Physicochemical Characteristics

Four benzodiazepine receptor agonists are commonly used in anesthesia: midazolam, diazepam, lorazepam, and temazepam (Fig. 23.8). The physicochemical characteristics of the benzodiazepines used in anesthesia are listed in Table 23.5. These six molecules are relatively small and are lipid soluble at physiologic pH.

Of the clinically used benzodiazepines, midazolam is the most lipid soluble *in vivo*,¹⁶⁷ but because of its pH-dependent solubility, it is water soluble when formulated in a buffered acidic medium (pH 3.5). The imidazole ring of midazolam accounts for its stability in solution and its lipophilicity due

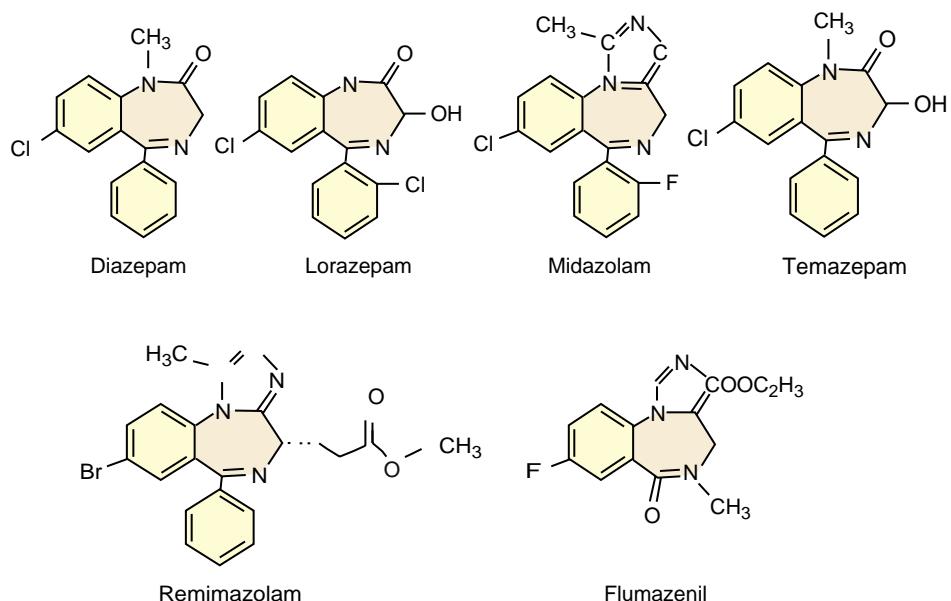


Fig. 23.8 The structures of six benzodiazepines.

TABLE 23.5 Physicochemical Characteristics of Benzodiazepines

	Molecular Weight	pK _a	Water Solubility	Lipid Solubility
	Da		g/L	Log P
Diazepam	284.7	3.4	0.051	2.801
Lorazepam	321.2	1.3	0.12	2.382
Temazepam	300.7	1.6, 11.7	0.28	2.188
Midazolam	325.8 (hydrochloride 362.2)	6.0	0.004 (2.0, pH 1)	3.798
Remimazolam	439.3 (besylate 597.5)	5.3	0.008 (7.5, pH 1)	3.724
Flumazenil	303.3	0.86	0.042	2.151

Water solubility values are in unbuffered water, maximal solubility at acidic pH in parenthesis. Data from <http://scifinder.cas.org>. pKa, dissociation constant. From Saari TI, Uusi-Oukari M, Ahonen J, Olkkola KT. Enhancement of GAB-Aergic activity: neuropharmacological effects of benzodiazepines and therapeutic use in anaesthesiology. *Pharmacol Rev*. 2011;63(1):243–267.

to rapid closing of the imidazole ring at physiological pH. The high lipophilicity of the compounds accounts for the rapid CNS effect and relatively large volumes of distribution.

Pharmacokinetics

The four benzodiazepines used in anesthesia are classified as short-acting (midazolam), intermediate-acting (lorazepam, temazepam), and long-acting (diazepam), according to their metabolism and plasma clearance (Table 23.6). The plasma disappearance curves of all benzodiazepines can be best described by a two- or three-compartment model.

Protein binding and volumes of distribution are not much different among these four benzodiazepines, but the clearance is significantly different. Factors that may influence the pharmacokinetics of benzodiazepines are age,

gender, race, enzyme induction, and hepatic and renal disease. In addition, the pharmacokinetics of the benzodiazepines are affected by obesity. The volume of distribution is increased as drug diffuses from the plasma into the adipose tissue. Although clearance is not altered, elimination half-lives are prolonged, owing to the increased volume of distribution and delayed return of the drug to the plasma in obese patients.¹⁶⁸ Generally, sensitivity to benzodiazepines in some patient groups, such as elderly patients, is greater despite relatively modest pharmacokinetic changes; factors other than pharmacokinetics must be considered when these drugs are used.

Midazolam: After oral ingestion midazolam is absorbed completely and the peak plasma concentration is achieved in 30 to 80 minutes.¹⁶⁹ The bioavailability is less than 50% due to a significant first-pass metabolism in the intestinal wall and the liver.^{169,170} After IV administration, midazolam is rapidly distributed, with a distribution half-life of 6 to 15 minutes.¹⁷⁰ The plasma protein binding is high: 94% to 98%.

The hepatic extraction ratio is low, ranging from 0.30 to 0.44, but is higher than the unbound free fraction of midazolam in plasma.¹⁶⁹ Thus, the protein binding is not a restrictive factor in drug extraction by the liver. With this intermediate hepatic extraction ratio, the metabolic clearance of midazolam may be susceptible both to changes in enzyme activity and to changes in hepatic blood flow.

The elimination half-life ranges from 1.7 to 3.5 hours.^{170,171} The plasma clearance ranges from 5.8 to 9.0 mL/kg/min and is higher compared to that of the other benzodiazepines. This is due to the fused imidazole ring, which is rapidly oxidized *in vivo*—much more rapidly than the methylene group of the diazepine ring of other benzodiazepines.¹⁷²

The pharmacokinetics of midazolam are affected by obesity, age, hepatic cirrhosis, and severity of critical illness. Because of its high lipophilicity (at physiological pH), midazolam distributes preferably to adipose tissue resulting in

TABLE 23.6 Pharmacokinetic Parameters of the Benzodiazepines

	Elimination half-life (h)	Clearance (mL/kg/min)	Vd (L/kg)	Plasma Protein Binding (%)	Reference
Midazolam	1.7-3.5	5.8-9.0	1.1-1.7	94-98	Dundee et al. (1984)
Diazepam	20-50	0.2-0.5	0.7-1.7	98-99	Greenblatt et al. (1980)
Lorazepam	11-22	0.8-1.5	0.8-1.3	88-92	Greenblatt et al. (1979)
Temazepam	6-8	1.0-1.2	1.3-1.5	96-98	Fraschini and Stankov (1993)
Remimazolam*	0.4	4521 mL/min	36.4 L	N.A.	Upton et al. (2010)
Flumazenil	0.7-1.3	13-17	0.9-1.9	40-50	Klotz and Kanto (1998)

*Noncompartmental analysis results from sheep.

N.A. is not available.

From Saari TI, Uusi-Oukari M, Ahonen J, Olkkola KT. Enhancement of GABAergic activity: neuropharmacological effects of benzodiazepines and therapeutic use in anesthesiology. *Pharmacol Rev*. 2011;63(1):243-267.

a prolonged elimination half-life in obese patients.¹⁶⁸ Liver cirrhosis reduces plasma clearance of midazolam due to decreased metabolism.¹⁷³

Midazolam is metabolized by CYP3A4 and CYP3A5¹⁷⁴ to 1-hydroxymethylmidazolam (= α -hydroxymidazolam) and 4-hydroxymidazolam.¹⁷⁵ These metabolites possess similar sedative activities compared to the parent compound and, when given over a longer time, these metabolites may accumulate. These metabolites are rapidly conjugated and excreted in the urine and have, like midazolam, a marked increase in peripheral volume of distribution in obese/overweight adolescents.^{175a} In comparison, 1-hydroxymethylmidazolam is less potent than its parent compound, the affinity to the receptor is about 60%, and weaker than that of midazolam. The metabolites are cleared more rapidly than midazolam itself, making them of little concern in patients with normal hepatic and renal function. In patients with renal impairment, though, they can cause profound sedation.¹⁷⁶

Diazepam: After oral ingestion the bioavailability is about 94%.¹⁷⁷ Time to peak plasma concentrations after oral ingestion is approximately 60 minutes.¹⁷⁸ Diazepam is extensively bound to plasma proteins; the volume of distribution ranges from 0.7 to 4.7 L/kg. The plasma clearance of diazepam ranges from 0.2 to 0.5 mL/min.¹⁷⁹

The pharmacokinetics of diazepam are affected by obesity and liver dysfunction and particularly by age. Increasing age reduces the clearance of diazepam significantly.¹⁸⁰

Metabolism occurs in the liver and is mediated mainly by CYP2C19 and CYP3A4. This accounts for 80% of the biotransformation of diazepam.¹⁸¹⁻¹⁸³ The metabolite N-desmethyldiazepam has pharmacodynamic characteristics similar to those of diazepam, but has a much slower elimination half-life extending to 200 hours. N-desmethyl-diazepam is further metabolized to oxazepam, which is also pharmacologically active.

Temazepam, another metabolite of diazepam, is mainly conjugated to temazepam glucuronide and a smaller part is demethylated to oxazepam and thereafter conjugated to oxazepam-glucuronide.¹⁸⁴

Lorazepam: The oral bioavailability is high, nearly 90%. Peak plasma concentrations are reached approximately 2 hours after oral ingestion, the mean elimination half-life is 15 hours, with a range of 8 to 25 hours.¹⁸⁵ Lorazepam has a large volume of distribution from 0.8 to 1.3 L/kg,¹⁸⁶ and it is highly bound to plasma proteins (>90%).

The clearance of lorazepam is 0.8 to 1.8 mL/kg/min. Lorazepam is conjugated in the liver to an inactive glucuronide and up to 70% is excreted in urine. The pharmacokinetics of lorazepam is little altered by age, and not altered by gender or renal disease, but clearance is decreased by hepatic dysfunction.¹⁸⁷

Remimazolam (CNS 7056)

Remimazolam, a new short-acting GABA_A receptor agonist with high affinity to the GABA receptor, is rapidly degraded in plasma by nonspecific esterases to its carboxylic acid metabolite CNS 7054. The incorporation of a carboxylic ester moiety into the benzodiazepine core of remimazolam renders it susceptible to nonspecific tissue esterases.¹⁸⁸ Preclinical studies in sheep showed a more rapid onset of action, greater depth of sedation, and more rapid recovery than midazolam. In sheep, remimazolam showed no dose-dependent depth of sedation like propofol.¹⁸⁹ In humans, remimazolam is eliminated by first-order pharmacokinetics, with no clear relationship registered between body weight and elimination clearance. Accumulation after prolonged infusion is unlikely. The clearance of remimazolam was rapid (overall mean clearance 70.3 ± 13.9 L/hr) and the volume of distribution moderately large (steady-state volume of distribution is 34.8 ± 9.4 L). No clear relation exists between body weight and systemic clearance. Level and duration of sedation are dose-dependent in humans.¹⁹⁰ Remimazolam trials conclude a safe administration for procedural sedation; it allows a faster recovery of neuropsychiatric function compared to midazolam. Possible benefit compared to propofol is the safe administration by endoscopists instead of healthcare providers trained in anesthesia.

Pharmacodynamics

Benzodiazepines act selectively at the GABA_A receptor, which mediates fast inhibitory synaptic transmission in the CNS. Benzodiazepines enhance the response to GABA by facilitating the opening of the GABA-activated chloride channels resulting in hyperpolarization. A series of compounds are candidates as endogenous ligand of the GABA_A receptor, such as diazepam binding inhibitor and other substances. This is an area of ongoing research.¹⁹¹

Translocator protein (TSPO, 18 kDa), first described as a peripheral binding site for benzodiazepines, which are not associated with GABA receptors, are expressed throughout the body and brain. While their precise function and pharmacologic significance remain only partly known, the TSPO role has many proposed functions depending on the tissue, like cholesterol transport, regulatory role in the heart, and immunomodulation related to inflammatory activation.¹⁹²

EFFECTS ON THE CENTRAL NERVOUS SYSTEM

All benzodiazepines have hypnotic, sedative, anxiolytic, amnesic, anticonvulsant, and centrally produced muscle-relaxing properties. They may differ to some extent in their potency and efficacy with regard to some of these pharmacodynamic actions (e.g., anticonvulsive action). The neurotransmitter GABA is an inhibitory neurotransmitter and controls the state of a chloride ion channel. Activation of this chloride ion channel results in neuronal hyperpolarization (increased membrane potential in the direction away from the threshold potential) and accounts for the classification of the GABA system as “inhibitory.” Benzodiazepines bind to their receptors with high affinity; the binding is stereospecific and saturable; the order of receptor affinity (potency) of three agonists is lorazepam > midazolam > diazepam. Midazolam is approximately 3 to 6 times, and lorazepam 5 to 10 times, as potent as diazepam.¹⁹³ As indicated previously, the mechanism of action of benzodiazepines is reasonably well understood.^{194,195} The interaction of benzodiazepine ligands with the GABA_A receptor is one of the few examples in which the complex systems of biochemistry, molecular pharmacology, genetic mutations, and clinical behavioral patterns can to some extent be explained. GABA_A subtypes mediate the different effects (amnesic, anticonvulsant, anxiolytic, and sleep).¹⁹⁵ The GABA_A receptor is a pentameric assembly built from 18 or more subunits (Fig. 23.9). Many different combinations of this pentameric assembly occur in different parts of the brain; linking this diversity to physiological function and pharmacologic specificity may be possible. The α -subunit of the pentameric complex occurs in six isoforms (α_1 - α_6).¹⁸⁷ Sedation, anterograde amnesia, and anticonvulsant properties are mediated via α_1 -subunits of the GABA_A receptors,¹⁹⁵ and anxiolysis and muscle relaxation are mediated via the α_2 -subunits. The “benzodiazepine receptors” are found in highest densities in the olfactory bulb, cerebral cortex, cerebellum, hippocampus, substantia nigra, and inferior colliculus, where lower densities in the striatum, lower brainstem, and spinal cord are found. Spinal cord benzodiazepine receptors can play an important role in analgesia; however, further elucidation of the mechanism of action of this drug class is required.¹⁹⁶ Intrathecal midazolam reduces excitatory GABA-mediated neurotransmission in interneurons, leading to a decrease in the excitability of spinal dorsal horn neurons.¹⁹⁶ A meta-analysis shows that intrathecal midazolam improves perioperative analgesia and reduces nausea and vomiting.¹⁹⁷

The benzodiazepines reduce the CMRO₂ in a dose-related manner. Midazolam and diazepam maintain a relatively normal ratio of CBF to CMRO₂.¹⁹⁸ Midazolam, diazepam, and lorazepam all increase the seizure initiation threshold to local anesthetics and decrease the mortality rate in mice exposed to lethal doses of local anesthetics. Midazolam has

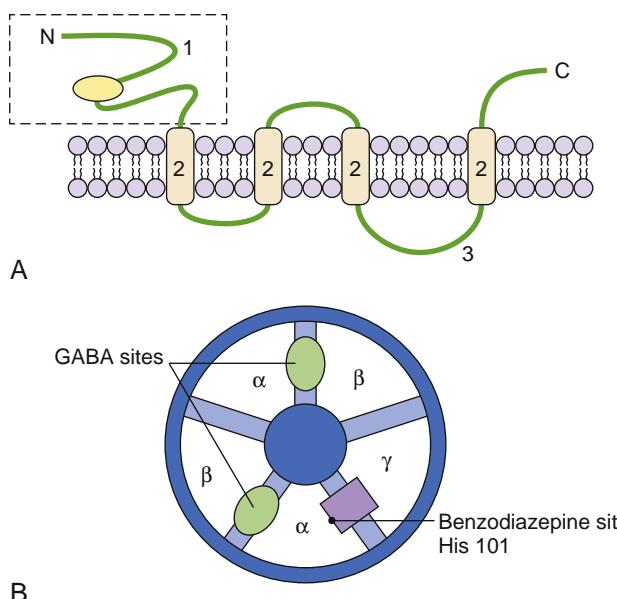


Fig. 23.9 Schematics of GABA_A receptor structure and function. (A) topography of a GABA_A receptor subunit partially embedded in the lipid bilayer. 1, N-terminal extracellular domain responsible for transmitter and ligand binding and coupling of the binding sites with ion channel. This part is also important for the assembly of various receptor subunits into functional receptors. 2, four transmembrane segments forming the anion channel are responsible for binding of hydrophobic ligands, ion selectivity, and channel binding sites. 3, intracellular loop between transmembrane segments 3 and 4 forms the domain for regulatory phosphorylation sites and for the intracellular factors anchoring the receptors in appropriate locations. (B) hypothetical binding sites for GABA and benzodiazepines ligands in a pentameric receptor complex. (From Saari TI, Uusi-Oukari M, Ahonen J, Olkkola KT. Enhancement of GABAergic activity: neuropharmacological effects of benzodiazepines and therapeutic use in anesthesiology. *Pharmacol Rev*. 2011;63[1]:243–267.)

neuroprotective effects by preventing lipid peroxidation and mitochondrial damage. There are indications in rats that the peripheral benzodiazepine receptor is involved in these actions.¹⁹⁹

Effects on the Respiratory System

Benzodiazepines, similar to most IV anesthetics, produce dose-related central respiratory system depression. The benzodiazepines affect respiration in two different ways. First, they have an effect on the muscular tone leading to an increased risk of upper airway obstruction.²⁰⁰ Second, they flatten the response of the respiratory curve to carbon dioxide.²⁰¹ In addition, sedative doses of midazolam depress the hypoxic ventilatory response in humans.²⁰²

Benzodiazepines and opioids produce additive or supra-additive (synergistic) respiratory depression, even though they act at different receptors.²⁰³ Old age, debilitating disease, and other respiratory depressant drugs increase the incidence and degree of respiratory depression and apnea by benzodiazepines.

Effects on the Cardiovascular System

The hypothalamic paraventricular nucleus (PVN) is an important site for autonomic and endocrine homeostasis of the cardiovascular system. The PVN integrates afferent stimuli to regulate blood volume; the rostral ventrolateral medulla is the dominant brain region for tonic regulation

of arterial blood pressure.²⁰⁴ Under normal circumstances, the sympathetic nervous system is tonically inhibited. This inhibition is dependent on GABAergic signaling and nitric oxide.²⁰⁵

Benzodiazepines, when used alone, have modest hemodynamic effects. The predominant hemodynamic change is a modest decrease in arterial blood pressure, resulting from a decrease in systemic vascular resistance. The mechanism by which benzodiazepines maintain relatively stable hemodynamics involves the preservation of homeostatic reflex mechanisms. The hemodynamic effects of midazolam and diazepam are dose related, however, there is a plateau plasma drug effect above which little change in arterial blood pressure occurs. The plateau plasma level for midazolam is 100 ng/mL, and that for diazepam is about 900 ng/mL. Heart rate, ventricular filling pressures, and cardiac output are maintained after induction of anesthesia with benzodiazepines. More recent studies using heart rate variability variables as measurements to evaluate the effect of benzodiazepines on autonomic neurocardiac regulation conclude a biphasic effect. First, the vagal tone reduces and second, the cardiac pacemaker may decrease using intravenous premedication doses. In patients with increased left ventricular filling pressures, diazepam and midazolam produce a “nitroglycerin-like” effect by decreasing the filling pressure and increasing cardiac output. Notably, the stress of endotracheal intubation and surgery are not blocked by midazolam.

Drug Interactions

PHARMACOKINETIC DRUG INTERACTIONS

The pharmacokinetics of benzodiazepines may be altered by drug interactions. As cytochrome P450 is often involved in the metabolism of the benzodiazepines, drugs inducing or inhibiting CYP function often cause alterations in the pharmacokinetics of the benzodiazepines.

CYP-mediated drug interactions have extensively been examined utilizing midazolam, which is almost completely metabolized by CYP, particularly CYP3A4.

The inhibition of CYP3A by concomitantly administered drugs like—among many others—the azole antifungal agents, results in significant inhibition of the metabolism of midazolam.²⁰⁶ Orally administered midazolam is especially affected by these inhibitors due to reduction of the first-pass metabolism elimination.²⁰⁷

Diazepam is primarily metabolized by CYP2C19 and CYP3A4. Different CYP2C19 alleles have varying activity, which results in ultra-rapid, extensive, intermediate, and poor metabolizer genotypes.^{208,209} Pharmacokinetics and pharmacodynamics vary among these different metabolizers.^{210,211} Strong inhibitors of CYP3A4 have a minor effect on the pharmacokinetics of diazepam.^{212,213} Inhibitors of CYP2C19 like omeprazole, fluvoxamine, and ciprofloxacin consequently increase the plasma half-life of diazepam substantially.²¹⁴⁻²¹⁶ The clearance of lorazepam is affected by probenecid and valproic acid, both of which decrease the formation clearance of lorazepam-glucuronide.^{217,218} Remimazolam is not metabolized by CYP-dependent mechanisms, which decreases the chances of significant drug interactions occurring.

PHARMACODYNAMIC DRUG INTERACTION

All benzodiazepines act on the CNS and interact with other drugs targeting the CNS, in particular those causing CNS depression.

In anesthetic practice, opioids are often combined with benzodiazepines, which interact in a synergistic manner.²¹⁹ The interaction between midazolam and ketamine is additive,²²⁰ while the interaction between the hypnotic effects of thiopental and midazolam and of propofol and midazolam are synergistic.^{20,221}

Uses

PREMEDICATION

Benzodiazepines are the most commonly applied drugs for premedication. The goals of this application are anxiolysis, sedation, amnesia, vagolysis, and sympatheticolysis, and reduction of PONV.²²² The amnestic effects are anterograde; retrograde memory is not affected.

Diazepam, lorazepam, and midazolam are given orally or intravenously for preoperative sedation. Midazolam is the most frequently used benzodiazepine for premedication in both adults and children.²²³ The usual oral dose for adults ranges from 7.5 to 15 mg for midazolam, from 5 to 10 mg for diazepam, and from 10 to 20 mg for temazepam.²²⁴ Many factors like age, ASA physical status, level of anxiety, and type and length of surgery determine the dose. Lorazepam is mostly used when a prolonged and intense anxiolysis is pursued, like in cardiac surgery. Typically, 2 to 4 mg lorazepam is administered orally 2 hours before anesthesia and surgery.²²⁵

For pediatric patients midazolam is available in several preparations (including a formulation for intranasal administration in some countries) and well tolerated. The dose is effective from 0.025 mg/kg and produces sedation and anxiolysis in 10 to 20 minutes.

Midazolam has minimal effects on respiration and oxygen saturation in adults, even in doses up to 1.0 mg/kg with a maximum of 20 mg.

Sedation

Relief of anxiety and lack of recall of unpleasant events during minor surgical and diagnostic procedures are the primary objectives of good sedation. Appropriately used sedation improves patient satisfaction.²²² Patients are seemingly conscious and coherent during sedation with benzodiazepines, yet they are amnesic for the procedure and events.²²⁶ For this use drugs should be given by titration; end points of titration are adequate sedation or dysarthria (Table 23.7). The onset of action is rapid with midazolam, usually with a peak effect reached within 2 to 3 minutes of administration; time to peak effect is slightly longer with diazepam and even longer still with lorazepam. The duration of action of these drugs are dose-dependent. Although the onset is more rapid with midazolam than with diazepam after bolus administration, the recovery is similar, probably because both drugs have similar early plasma decay (redistribution) patterns.²²⁷ (also see Fig. 23.10). With lorazepam, sedation and particularly amnesia are slower in

onset and are longer lasting than with the other two benzodiazepines.²²⁸ Lorazepam is particularly unpredictable with regard to duration of amnesia, and this is undesirable in patients who wish or need to have recall in the immediate postoperative period. The degree of sedation, the reliable amnesia, and the preservation of respiratory and hemodynamic function are better with benzodiazepines than with other sedative-hypnotic drugs used for conscious sedation. When midazolam is compared with propofol for sedation during procedures, the two are generally similar except that emergence or wake-up is more rapid with propofol. Sedation with propofol is safe in the hands of well-trained non-anesthetic professionals.^{229,230}

There are studies showing that remimazolam has a favorable profile as a sedative for upper gastrointestinal endoscopy in patients as the time to recovery was shorter and more consistent than that observed after the use of midazolam.^{188,190} The use of midazolam for sedation during regional and epidural anesthesia requires vigilance with regard to depth of sedation and respiratory function.²³¹

Two studies report the use of midazolam during cesarean section either for sedation in preeclamptic parturients or prevention of nausea and vomiting; they showed that

a single IV dose of midazolam was a safe practice, with no detriment in Apgar scores, neurobehavioral scores, continuous oxygen saturation, or the ability of the mother to recall the birth events.²³² Nitsun and associates found that 0.005% of the maternal dose of midazolam is transferred into the breast milk during a 24-hour milk collection.²³³ Although verification of these findings is needed, they highlight an important clinical use of midazolam that may be safe for mother and infant.

Sedation for longer periods, such as in the ICU, can also be accomplished with benzodiazepines. Prolonged infusion may result in accumulation of drug and, in the case of midazolam, significant concentration of the active metabolite. Reviews have pointed out both concerns and advantages of benzodiazepine sedation.²³⁴ The main advantages are the amnesia and hemodynamic stability, where the disadvantage is the potential lingering sedative effect after termination of the infusion when compared with propofol and a higher prevalence of delirium compared to dexmedetomidine. In 2013, the Society of Critical Care Medicine's (SCCM) American College of Critical Care Medicine (ACCM) published a revised version of its pain, agitation, and delirium (PAD) clinical practice guidelines for adult ICU patients. These guidelines suggest that sedation strategies using non-benzodiazepine sedatives may be preferred over sedation with benzodiazepines, either midazolam or lorazepam, to improve clinical outcome in mechanically ventilated ICU patients.²³⁵ To prevent overdosing and prolonged mechanical ventilation, evidence-based sedation algorithms have evolved. Daily interruption of sedation has not proven to decrease the time to extubation of the trachea or length of hospital stay.²³⁶

Induction and Maintenance of Anesthesia

Midazolam is the benzodiazepine of choice for induction of anesthesia. Numerous factors influence the rapidity of action of midazolam and the other benzodiazepines when used for induction of general anesthesia, including dose, speed of injection, degree of premedication, age, ASA physical status, and concurrent anesthetic drugs. The usual induction dose of midazolam is 0.1 to 0.2 mg/kg in premedicated patients, and up to 0.3 mg/kg in unpremedicated patients. The onset of anesthesia is within 30 to 60 seconds. The half-time of equilibrium between the plasma concentration and the EEG effects is about 2 to 3 minutes.²³⁷

Elderly patients require smaller doses of midazolam than younger patients (Fig. 23.11).²³⁸

When midazolam is combined with other anesthetic drugs (coinduction), often a synergistic interaction occurs, similar to that seen with propofol. This synergy is observed when midazolam is used with opioids or other hypnotics, similar to propofol in combination with opioids (Fig. 23.12).^{20,52,239}

Emergence time is related to the dose of midazolam and to the dose of adjuvant anesthetic drugs.

Benzodiazepines lack analgesic properties and must be used with other anesthetic drugs to provide sufficient analgesia; however, as maintenance anesthetic drugs during general anesthesia, benzodiazepines provide hypnosis and amnesia. The amnesic period after an anesthetic dose is about 1 to 2 hours.

TABLE 23.7 Uses and Doses of Intravenous Benzodiazepines

	Midazolam	Diazepam	Lorazepam
Induction	0.05-0.15 mg/kg	0.3-0.5 mg/kg	0.1 mg/kg
Maintenance	0.05 mg/kg prn	0.1 mg/kg prn	0.02 mg/kg prn
1 μ g/kg/min			
Sedation*	0.5-1 mg repeated	2 mg repeated	0.25 mg repeated
0.07 mg/kg IM			

*Incremental doses given until desired degree of sedation is obtained.
IM, Intramuscular; prn, as required to keep patient hypnotic and amnesic.
From Reves JG, Glass P, Lubarsky DA, et al. Intravenous anesthetics. In: Miller RD, Eriksson LI, Fleischner LA, et al, eds. *Miller's Anesthesia*, 7th ed. Philadelphia: Churchill Livingstone; 2010: 719-768.

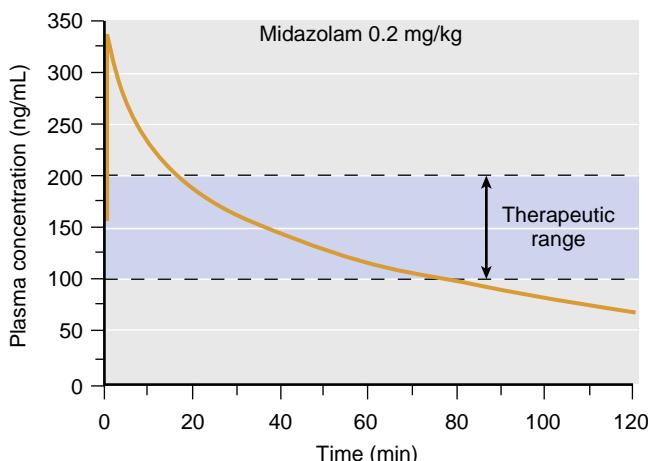


Fig. 23.10 Simulated time course of plasma levels of midazolam after an induction dose of 0.2 mg/kg. Plasma levels required for hypnosis and amnesia during surgery are 100 to 200 ng/mL, with awakening usually occurring at levels less than 50 ng/mL.

A plasma level of more than 50 to 100 ng/mL occurs when used with adjuvant opioids (e.g., fentanyl) or inhaled anesthetics (e.g., nitrous oxide, volatile anesthetics) by a bolus initial dose of 0.05 to 0.15 mg/kg and a continuous infusion of 0.25 to 1 μ g/kg/min.²⁴⁰ This plasma level is sufficient to keep the patient asleep and amnesic but arousable at the end of surgery. Smaller infusion doses may be required in some patients or in combination with opioids. Midazolam, diazepam, and lorazepam accumulate in the blood after repeated bolus administrations or with continuous infusion. If the benzodiazepines do accumulate with repeated administration, prolonged arousal time can be anticipated. This is less of a problem with midazolam than with diazepam and lorazepam because of the shorter context-sensitive half-time and greater clearance of midazolam. Remimazolam might be a good alternative; it is

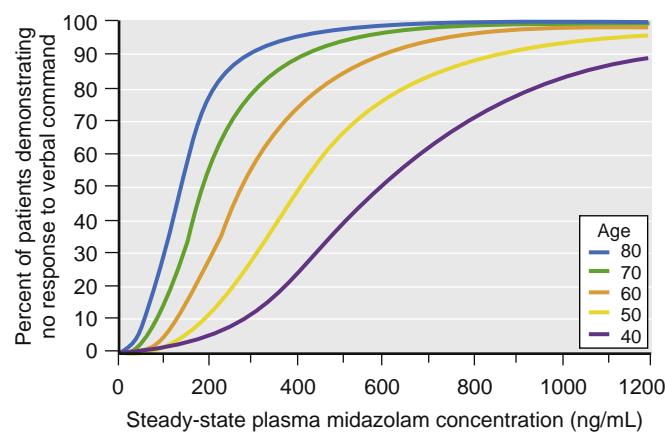


Fig. 23.11 Spectrum of the intrinsic activities of benzodiazepine receptor ligands, which range from agonists to inverse agonists. Structures of agonist, partial agonist, antagonist, partial inverse agonist, and inverse agonist compounds are shown. Intrinsic activity is greatest among agonists and is least among inverse agonists. Intrinsic activities are schematically indicated as positive by a plus sign and as negative by a minus sign, with 0 indicating a lack of intrinsic activity. GABA, γ -aminobutyric acid. (Redrawn with modification from Mohler H, Richards JG. The benzodiazepine receptor: a pharmacological control element of brain function. *Eur J Anaesthesiol*. 1988;Suppl 2:15–24.)

rapidly metabolized and has a faster recovery profile than midazolam in sheep.^{189,190}

Nausea and Vomiting Prophylaxis

Numerous studies have highlighted the role that benzodiazepines, and specifically midazolam, may play in the prevention of PONV. A recent meta-analysis on the effect of intravenous midazolam on PONV concludes a significant decrease in overall PONV and rescue antiemetic drug. Jung and colleagues found that in women undergoing middle ear surgery, IV midazolam, 0.075 mg/kg after induction of anesthesia, reduced the incidence of PONV and the need for rescue antiemetics with no difference from placebo in pain intensity or drowsiness.²⁴¹ Furthermore, the combination of midazolam with dexamethasone proved more effective in preventing PONV than midazolam alone.²⁴² The incidence of PONV after minor gynecologic or urologic surgery was the same when comparing IV ondansetron, 4 mg, and IV midazolam, 2 mg.²⁴³

In children, IV midazolam, 0.05 mg/kg, reduced PONV significantly after pediatric (4–12 years old) strabismus surgery compared with placebo or IV dexamethasone 0.5 mg/kg. No child vomited with midazolam alone or with the midazolam dexamethasone combination.^{244,245}

Finally, in a 2010 three-arm, placebo-controlled, double-blind clinical trial, Fuji and associates compared midazolam 0.050 mg/kg with 0.075 mg/kg in patients undergoing laparoscopic gynecologic surgery regarding PONV prophylaxis. The two doses of midazolam were not significantly different with regard to PONV (30% vs. 27% of patients experienced PONV) and both proved better than placebo (67%).²⁴⁶

Side Effects and Contraindications

Benzodiazepines have limited allergenic effects and do not suppress the adrenal gland. The most significant side effect with midazolam is respiratory depression. The major side effects of lorazepam and diazepam in addition to respiratory depression are venous irritation and thrombophlebitis, problems related to aqueous insolubility and requisite solvents.¹⁶⁵ When used as sedative or for induction and

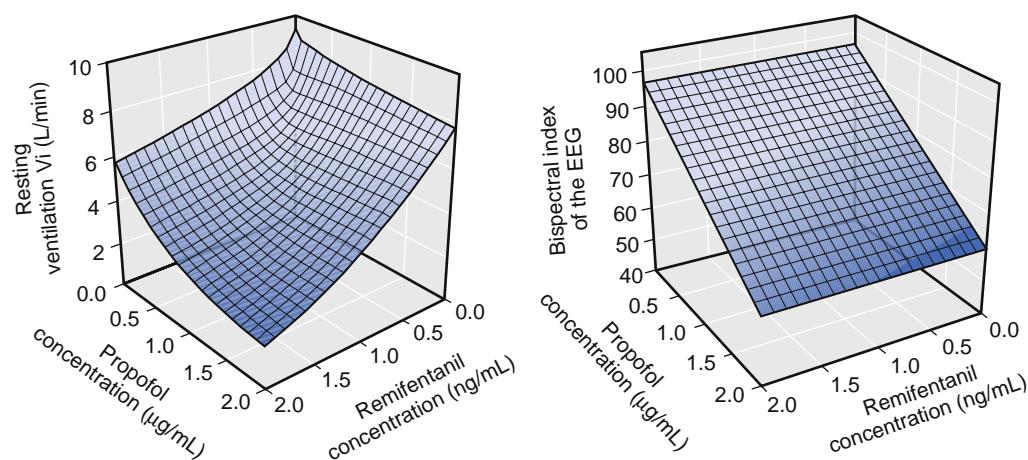


Fig. 23.12 Response surface modeling of the interaction of remifentanil and propofol on resting ventilation and the bispectral index of the electroencephalogram (BIS). Population response surface showing that the propofol-remifentanil interaction on respiration is synergistic and on BIS is inert since remifentanil had no effect on bispectral index irrespective of the propofol concentrations. Over this dose range, propofol causes a linear decrease in bispectral index with a 25% decrease occurring at 1.4 μ g/mL. (From Nieuwenhuijs DJ, Olofsen E, Romberg RR, et al. Response surface modeling of remifentanil-propofol interaction on cardiorespiratory control and bispectral index. *Anesthesiology*. 2003; 98:312–322.)

maintenance of anesthesia, benzodiazepines may produce an undesirable degree or prolonged interval of postoperative amnesia, sedation, and, rarely, respiratory depression. These residual effects can be reversed with flumazenil.²⁴⁷

Flumazenil

Flumazenil (Anexate, Romazicon) is the first benzodiazepine antagonist approved for clinical use.²⁴⁸ It is a benzodiazepine receptor ligand with high affinity, great specificity, and by definition minimal intrinsic effect. Flumazenil, similar to the agonists it replaces at the benzodiazepine receptor, interacts with the receptor in a concentration-dependent manner. It is a competitive antagonist at the benzodiazepine receptor and produces antagonism that is reversible and surmountable. In humans, flumazenil has minimal agonist activity, which means that its benzodiazepine receptor agonist effects are very weak, significantly less than those of clinical agonists.²⁴⁹ Flumazenil, similar to all competitive antagonists at receptors, does not displace the agonist, but rather occupies the receptor when an agonist dissociates from the receptor. The half-time (or half-life) of a receptor-ligand bond is a few milliseconds to a few seconds, and new ligand receptor bonds are immediately formed. This dynamic situation accounts for the ability of either an agonist or an antagonist to readily occupy the receptor. The ratio of agonist to total receptors produces the effects of the agonist drug, but the antagonist can alter this ratio, depending on its concentration and dissociation constant. Flumazenil, which is an avid (high-affinity) ligand, replaces a relatively weak agonist, such as diazepam, as long as it is given in sufficient dose. Flumazenil is rapidly metabolically cleared, however, and the proportion of receptors occupied by the agonist then increases again, and the potential for rebound sedation and respiratory suppression exists (Fig. 23.13). This situation is

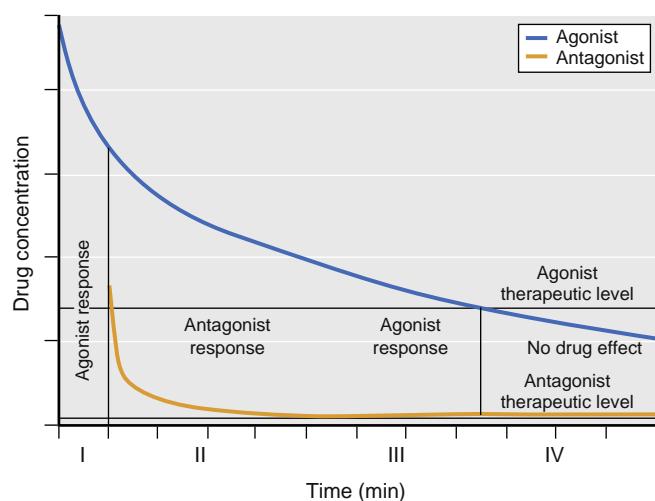


Fig. 23.13 Schematic representation of the interaction of a short-acting antagonist with a longer-acting agonist resulting in resedation. The upper curve shows disappearance of agonist from blood, and the lower curve shows disappearance of antagonist from plasma. Four conditions are represented: I, agonist response; II, antagonist response (the antagonist reverses the agonist effect); III, agonist response (resedation or resumption of agonist response with disappearance of short-lasting antagonist); and IV, no drug effect, with disappearance of agonist and antagonist (both drugs are below the therapeutic level).

less likely to occur when flumazenil is used to reverse midazolam, which has a more rapid clearance than other benzodiazepine agonists. Another important finding is that in the presence of extremely large doses of agonist (e.g., when a mistake in dosing has occurred, or suicide by means of an overdose is attempted), a small dose of flumazenil attenuates the deep CNS depression (loss of consciousness, respiratory depression) by reducing the fractional receptor occupancy by the agonist without decreasing the agonist effects that occur at low fractional receptor occupancy (drowsiness, amnesia).

Conversely, large doses of flumazenil in the presence of small doses of agonist completely reverse all the agonist effects. Flumazenil can precipitate withdrawal symptoms in animals or in humans physically dependent on a benzodiazepine receptor agonist.²⁵⁰ However, this is not a problem when flumazenil is used to reverse clinical effects of benzodiazepine receptor agonists applied in the practice of anesthesia.

PHYSICOCHEMICAL CHARACTERISTICS

Flumazenil is similar to midazolam and other classic benzodiazepines except for the absence of the phenyl group, which is replaced by a carbonyl group (see Fig. 23.8). It forms a colorless, crystalline powder; has a dissociation constant of 1.7; and has weak but sufficient water solubility to permit its preparation in aqueous solution. Its octanol/aqueous buffer (pH 7.4) partition coefficient is 14, showing moderate lipid solubility at pH 7.4.²⁵¹

PHARMACOKINETICS

Flumazenil, similar to the other benzodiazepines, is completely (99%) metabolized in the liver; is rapidly cleared from the plasma; and has three known metabolites: *N*-desmethylflumazenil, *N*-desmethylflumazenil acid, and flumazenil acid.²⁵² The metabolic end product, that is, flumazenil acid, has no pharmacologic activity. The major metabolites identified in urine are the de-ethylated free acid and its glucuronic acid conjugate. Flumazenil is a short-lived compound. **Box 23.2** includes a summary of its pharmacokinetics, which are described in various clinical settings. The volume of distribution is high and extravascular distribution is rapid.

Compared with most benzodiazepine receptor agonists, flumazenil has a very rapid clearance and short elimination half-life.²⁵³ Only remimazolam has a more rapid clearance and shorter half-life. The plasma half-life of flumazenil is

BOX 23.2 Uses and Doses of Flumazenil

Reversal of benzodiazepines	0.2 mg repeated up to 3 mg
Diagnosis in coma	0.5 mg repeated up to 1 mg

*The dose required to reverse each benzodiazepine (BZD) depends on residual BZD and the particular BZD (i.e., higher doses are required for more potent BZDs) (see text).

[†]The degree of reversal should be titrated by repeating 0.2-mg increments every 1 to 2 min until the desired level of reversal is achieved.

From Reves JG, Glass P, Lubarsky DA, et al. Intravenous anesthetics. In Miller RD, Eriksson LI, Fleischer LA, et al, eds. *Miller's Anesthesia*, 7th ed. Philadelphia: Churchill Livingstone; 2010: 719–768.

about 1 hour—it is the shortest lived of all benzodiazepines used in anesthetic practice. The rapid blood clearance of flumazenil approaches hepatic blood flow, a finding that indicates that liver clearance partially depends on hepatic blood flow. Compared with other benzodiazepines, flumazenil has a high proportion of unbound drug; plasma protein binding is about 40%. The potential exists for the antagonist to be cleared, leaving sufficient concentrations of agonist at the receptor site to cause resedation.²⁵⁴ To maintain a constant therapeutic blood level over a prolonged time, either repeated administration or a continuous infusion is required. An infusion rate of 30 to 60 μ g/min (0.5-1 μ g/kg/min) has been used for this purpose.²⁵⁵

PHARMACODYNAMICS

When given in the absence of a benzodiazepine receptor agonist, flumazenil has little discernible CNS effect. When given to healthy subjects and patients in clinically relevant doses, flumazenil has no effect on the EEG or cerebral metabolism. Flumazenil is free of anticonvulsant properties, and reverses the anticonvulsant properties of benzodiazepines in local anesthetic-induced seizures.²⁵⁶ When administered to patients who have benzodiazepine-induced CNS depression, flumazenil produces rapid and dependable reversal of unconsciousness, respiratory depression, sedation, amnesia, and psychomotor dysfunction.²⁵⁷ Flumazenil can be given before, during, or after the agonist to block or reverse the CNS effects of the agonist.

Flumazenil has successfully reversed the effects of benzodiazepines like midazolam, diazepam, lorazepam, and flunitrazepam. It has also been used successfully to reverse the effects of chloralhydrate and cannabis intoxication in children,^{258,259} carbamazepine and alcohol overdose,²⁶⁰ and antihistamines overdose.²⁶¹ The onset is rapid, with peak effect occurring in 1 to 3 minutes, which coincides with the detection of C-flumazenil in the human brain.²⁵⁷ Flumazenil reverses the agonist by replacing it at the benzodiazepine receptor, and its onset and duration are governed by the law of mass action. When flumazenil is given in the presence of agonists, there are significant respiratory effects because it reverses respiratory depression caused by the agonists (e.g., when given to volunteers made apneic with midazolam). For example, the reversal of midazolam-induced (0.13 mg/kg) respiratory depression with flumazenil (1 mg) lasts 3 to 30 minutes. Other agonists and other doses would have different durations of antagonism of respiratory depression.

Incremental doses up to 3 mg intravenously in patients with ischemic heart disease had no significant effect on cardiovascular variables.^{257,262} Administration of flumazenil to patients given agonists is remarkably free of cardiovascular effects, in contrast to the experience of opioid reversal with naloxone.²⁶³ Although flumazenil does reverse sedation, it does not increase blood concentrations of catecholamines. However, catecholamine levels may increase when arousal is more rapid after flumazenil.²⁶⁴ The reversal of sedation by midazolam with flumazenil also restores the attenuated cardiac baroreflex function.²⁶⁵

In healthy subjects, flumazenil did not alter intraocular pressure but reversed the decrease in intraocular pressure observed after administration of midazolam (Romazicon package insert; www.fda.gov).

Uses and Doses

Application of a benzodiazepine antagonist (see Box 23.2) includes the diagnostic and therapeutic reversal of benzodiazepine receptor agonists. For diagnostic use in suspected benzodiazepine overdose, flumazenil may be given in incremental IV doses of 0.2 to 0.5 mg up to 3 mg. More commonly in anesthesia, flumazenil is used to reverse the residual sedation of a patient after administration of a benzodiazepine for premedication of a short surgical procedure, conscious sedation, or for general anesthesia. Flumazenil reliably reverses the sedation, respiratory depression, and amnesia caused by benzodiazepines. There are differential reversal effects on the different agonist actions. Flumazenil tends to reverse the hypnotic and respiratory effects more than the amnesic effects of the benzodiazepine agonist.^{266,267}

The dose varies with the particular benzodiazepine being reversed, and the duration of reversal depends on the kinetics of the agonist and of flumazenil. Surveillance is recommended if a long-lasting benzodiazepine is reversed with a single administration of flumazenil because of the relatively short-lived effect. If a patient shows no signs of recurrent sedation within 2 hours after a 1-mg reversal dose of flumazenil, serious recurrent sedation at a later time is unlikely. Flumazenil may be administered by continuous infusion to prevent recurrent sedation by longer lasting benzodiazepine receptor agonists. The pharmacokinetic profile of flumazenil is unaltered in the presence of benzodiazepine agonists (diazepam, flunitrazepam, lorazepam, midazolam) and vice versa.

Side Effects and Contraindications

Flumazenil has been given in large oral and IV doses with remarkably few toxic reactions.²⁵⁷ It is free of local or tissue irritant properties, and there are no known organotoxicities. Similar to all benzodiazepines, it apparently has a high safety margin, probably higher than the safety margins of the agonists, because it does not produce prominent CNS depression. In patients using large doses of benzodiazepines over several weeks or longer, the administration of flumazenil may elicit symptoms of benzodiazepine withdrawal, including seizures.

Phencyclidines (Ketamine)

HISTORY

Ketamine (Ketalar) was synthesized in 1962 by Stevens and was first used in humans in 1965 by Corssen and Domino. Ketamine was released for clinical use in 1970 and is still used in various clinical settings. It produces dissociative anesthesia rather than generalized depression of the CNS through antagonistic actions at the phencyclidine (PCP) site of the N-methyl-D-aspartate receptor (NMDAR). Ketamine is a racemic mixture of the isomers R(-)-ketamine and S(+)-ketamine. It usually does not depress the cardiovascular and respiratory systems, but it does possess some of the adverse psychological effects found with the other phencyclidines.²⁶⁸ The S(+)-isomer (Ketanest) is 3 to 4 times more potent as an analgesic with a faster clearance and recovery and with fewer psychomimetic side effects. Still, S-ketamine produces—besides analgesia—psychotropic effects, cognitive impairment, memory impairment, and a reduced

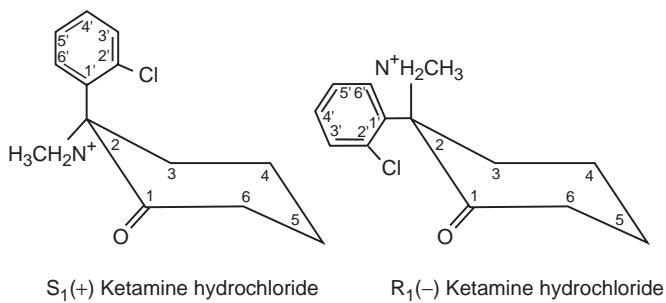


Fig. 23.14 Stereoisomers of ketamine as it is formulated.

reaction time. Interest in ketamine has increased more recently because of its effects on hyperalgesia and opiate tolerance, use in chronic pain states, potential neuroprotective effects, increasing popularity of total IV anesthesia, and the availability in some countries of $S(+)$ ketamine.²⁶⁹ Lastly, ketamine receives growing interest because of its antidepressant effects.

PHYSICOCHEMICAL CHARACTERISTICS

Ketamine (Fig. 23.14) has a molecular weight of 238 kD, is partially water soluble, and forms a white crystalline salt with a pK_a of 7.5. It has a lipid solubility 5 to 10 times that of thiopental. Ketamine is only 12% bound to proteins. Its bioavailability is 93% after parenteral administration but only 20% after oral use, due to its high first-pass metabolism.²⁷⁰

PHARMACOKINETICS

Ketamine is metabolized by hepatic microsomal enzymes.^{271,272} The major pathway involves *N*-demethylation to form norketamine (metabolite I), which is then hydroxylated to hydroxynorketamine, which is further conjugated to water-soluble glucuronide derivates and excreted in the urine. The activity of the principal metabolites of ketamine has not been well studied, but norketamine (metabolite I) has significantly less (20%-30%) activity than the parent compound. More recent modeling of norketamine suggests that it contributes in prolonging the analgesia provided by either a bolus or infusion of ketamine, although this conclusion is being questioned.^{271,273,274} In contrast to previous reports, S -norketamine may have a negative contribution to S -ketamine-induced analgesia but shows absence of contribution to the cognitive impairment. This may explain the observation of ketamine-related excitatory phenomena (such as hyperalgesia and allodynia) upon the termination of ketamine infusions.^{271,273,274}

Ketamine's pharmacokinetics have been examined after bolus administration of anesthetizing doses (2-2.5 mg/kg IV), after a subanesthetic dose (0.25 mg/kg IV), and after continuous infusion (steady-state plasma level 2000 ng/mL).

Regardless of the dose, ketamine plasma disappearance can be described by a two-compartment model. Table 23.1 contains the pharmacokinetic values from bolus administration studies. Of note is the rapid distribution reflected in the relatively brief distribution half-life of 11 to 16 minutes (Fig. 23.15). The high lipid solubility of ketamine is reflected in its large volume of distribution of nearly 3 L/kg.^{272,275} Clearance

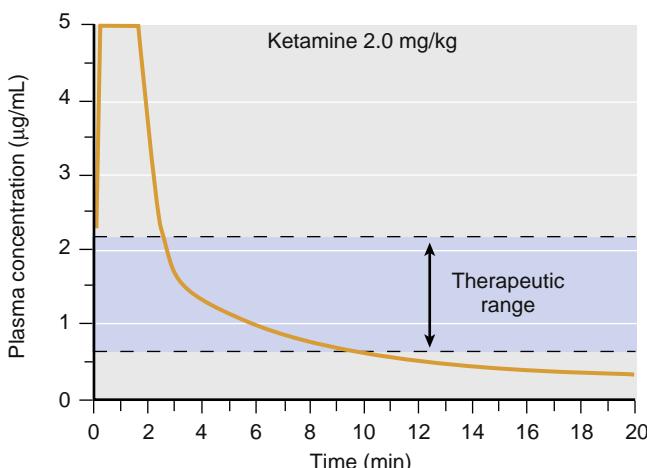


Fig. 23.15 Simulated time course of plasma levels of ketamine after an induction dose of 2 mg/kg. Plasma levels required for hypnosis and amnesia during surgery are 0.7 to 2.2 μ g/mL, with awakening usually occurring at levels less than 0.5 μ g/mL.

also is high, 890 to 1227 mL/min, which accounts for the short elimination half-life of 2 to 3 hours. The mean total body clearance (1.4 L/min) is approximately equal to liver blood flow. Low-dose alfentanil increases the volume of distribution and clearance of ketamine. In addition, alfentanil increases the distribution of ketamine into the brain. The pharmacokinetic model of Clements provided the best accuracy when used to administer low-dose ketamine to volunteers using a target-controlled infusion device. The pharmacokinetics of the two isomers is different. $S(+)$ ketamine has a larger elimination clearance and larger volume of distribution than $R(-)$ ketamine. When the pharmacokinetics of $S(+)$ ketamine were tested in a target-controlled infusion device for procedures of 1 hour and in combination with propofol, the authors found that the accuracy of the pharmacokinetic parameters was improved with a much smaller V_c^* (167 mL/kg).²⁷⁶ They also noted that ketamine clearance was not normally distributed, and this was not related to age. The $S(+)$ enantiomer also seems to be more potent in suppressing the EEG than either $R(-)$ or the racemic mixture. Ketamine is increasingly being given by alternative routes, especially orally and via an intranasal spray. Administration by either of these routes is subject to significant first-pass metabolism. The bioavailability via oral administration is 20% to 30%, and via the intranasal route is approximately 40% to 50%. In clinical and experimental studies hyperalgesic responses have been noted after the withdrawal of $S(+)$ -ketamine.^{273-275,277,278} Furthermore, no delay between concentration and effect has been observed for any of the antinociceptive end points. This indicates an almost immediate passage of $S(+)$ -ketamine across the blood-brain barrier and rapid receptor kinetics.

Pharmacodynamics

EFFECTS ON THE CENTRAL NERVOUS SYSTEM

Ketamine produces dose-related unconsciousness and analgesia. Ketamine acts at multiple receptors including the NMDAR, opioid receptors, and monoaminergic receptors.

* V_c (central compartment volume of a three compartment model).

At high ketamine concentrations, sigma opioid receptors are also affected, muscarinic receptors are blocked, and GABAergic neurotransmission is facilitated. Its most important action is the inhibition of NMDAR-mediated glutameric input to the GABAergic system leading to a changing excitatory activity in the cortex and limbic system that in the end results in unconsciousness. At the spinal cord level, ketamine has potent antinociceptive effects on NMDAR and inhibits acetylcholine release.²⁷³⁻²⁷⁵ The anesthetized state has been termed *dissociative anesthesia* because patients who receive ketamine alone appear to be in a cataleptic state, in contrast with other states of anesthesia that resemble normal sleep. Patients anesthetized with ketamine have profound analgesia, but keep their eyes open and maintain many reflexes. Corneal, cough, and swallow reflexes all may be present, but should not be assumed to be protective. There is no recall of surgery or anesthesia, but amnesia is not as prominent with ketamine as with the benzodiazepines. Because ketamine has a low molecular weight, a pK_a near the physiologic pH, and relatively high lipid solubility, it crosses the blood-brain barrier rapidly and has an onset of action within 30 to 60 seconds of administration. The maximal effect occurs in about 1 minute.

After ketamine administration, pupils dilate moderately, and nystagmus occurs. Lacrimation and salivation are common, as is increased skeletal muscle tone, often with coordinated but seemingly purposeless movements of the arms, legs, trunk, and head. Although there is great interindividual variability, plasma levels of 0.6 to 2 $\mu\text{g}/\text{mL}$ are considered the minimum concentrations for general anesthesia; children may require slightly higher plasma levels (0.8-4 $\mu\text{g}/\text{mL}$). The duration of ketamine anesthesia after a single IV administration of a general anesthetic dose (2 mg/kg) is 10 to 15 minutes (see Fig. 23.15), and full orientation to person, place, and time occurs within 15 to 30 minutes. The S(+) enantiomer enables quicker recovery (by a couple of minutes) than the racemic mixture.^{279,280} This is due to the smaller dose necessary to produce an equianesthetic effect and to the 10% faster hepatic biotransformation. Because there is a good correlation between blood concentration of ketamine and CNS effect, the relatively short duration of action of ketamine is probably due to its redistribution from the brain and blood to the other tissues in the body.

Concomitant administration of benzodiazepines, which is a common practice, may prolong the effect of ketamine. When used in combination with a benzodiazepine, the S(+) enantiomer was no different in terms of awareness at 30 minutes, but it was significantly better at 120 minutes than the racemic mixture. Analgesia occurs at considerably lower blood concentrations than loss of consciousness.

Ketamine provides important postoperative analgesia. The plasma level at which pain thresholds are elevated is 0.1 $\mu\text{g}/\text{mL}$ or greater.^{277,281,282} This means there is a considerable period of postoperative analgesia after ketamine general anesthesia, and subanesthetic doses can consequently be used to produce analgesia. Ketamine inhibits nociceptive central hypersensitization. Ketamine also attenuates acute tolerance after opiate administration. The NMDAR plays an important role in the induction of hyperalgesia and antinociceptive tolerance as induced by opioids. Preventive ketamine administration may thus

prevent central sensitization and long-lasting enhancement in pain sensitivity as induced by opioids. Ketamine, just as other NMDAR antagonists, may thus prevent opioid-induced hyperalgesia.²⁸³ The primary site of CNS action of ketamine seems to be the thalamoneocortical projection system. The drug selectively depresses neuronal function in parts of the cortex (especially association areas) and thalamus, while stimulating parts of the limbic system, including the hippocampus. This process creates what is termed a *functional disorganization* of nonspecific pathways in midbrain and thalamic areas. Ketamine acts via antagonism of the excitatory glutamatergic NMDA receptor. The NMDA receptor has a high expression in the temporal cortex, hippocampus, basal ganglia, cerebellum, and brainstem, all regions significantly affected by ketamine. There is also evidence that ketamine depresses transmission of impulses in the medial medullary reticular formation, which is important for transmission of the affective-emotional components of nociception from the spinal cord to higher brain centers. In volunteers experiencing heat pain, functional magnetic resonance imaging (MRI) studies showed ketamine produced a dose-dependent effect on pain processing by decreasing activation of the secondary somatosensory cortex (S2), insula, and anterior cingulate cortex. Ketamine occupies opiate receptors in the brain and spinal cord, and this property could account for some of the analgesic effects.^{284,285} The S(+) enantiomer has some opioid μ -receptor activity, accounting for part of its analgesic effect. NMDA receptor interaction may mediate the general anesthetic effects and some analgesic actions of ketamine. The spinal cord analgesic effect of ketamine is postulated to be due to inhibition of dorsal horn wide dynamic range neuronal activity. In a resting state fMRI study, low-dose ketamine induced connectivity changes in brain areas involved in motor function, psychedelic effects, and pain processing. Ketamine's analgesic effect may arise from multiple pathways; a decreased connectivity in regions of the pain matrix responsible for the perception of pain (pain sensing) and the affective processing of pain. In addition, ketamine affected connectivity in brain areas involved in endogenous pain inhibition.^{286,287}

Although some drugs have been used to antagonize ketamine, no specific receptor antagonist reverses all the CNS effects of ketamine.

Ketamine increases cerebral metabolism, CBF, and ICP. Because of its excitatory CNS effects, which can be detected by generalized EEG development of theta wave activity and by petit mal seizure-like activity in the hippocampus, ketamine increases CMRO_2 . There is an increase in CBF, which appears higher than the increase in CMRO_2 would mandate. With the increase in CBF and the generalized increase in sympathetic nervous system response, there is an increase in ICP after ketamine. The increase in CMRO_2 and CBF can be blocked by the use of thiopental or diazepam. Cerebrovascular responsiveness to carbon dioxide seems to be preserved with ketamine; reducing PaCO_2 attenuates the increase in ICP after ketamine.

S(+) ketamine may influence the expression of apoptosis-regulating proteins in rat brains 4 hours after cerebral ischemia/reperfusion. The neuroprotection observed with ketamine may involve antiapoptotic mechanisms in addition to reducing necrotic cell death.

In contrast, ketamine and other anesthetics like propofol and volatile anesthetics, accentuate apoptosis in the brain of newborn animals and cause changes in the morphology of dendritic spines. This finding has sparked controversy over the use of ketamine in neonates. An editorial in the journal *Anesthesiology* and the Anesthetic and Life Support Drugs Advisory Committee of the FDA cautioned changing clinical practice based on present available data.

Ketamine, similar to other phencyclidines, produces undesirable psychological reactions, which occur during awakening from ketamine anesthesia and are termed *emergence reactions*. The common manifestations of these reactions, which vary in severity and classification, are vivid dreaming, extracorporeal experiences (sense of floating out of body), and illusions (misinterpretation of a real, external sensory experience). These incidents of dreaming and illusion are often associated with excitement, confusion, euphoria, and fear. They occur in the first hour of emergence and usually abate within 1 to several hours. The psychic emergence reactions occur secondary to ketamine-induced depression of auditory and visual relay nuclei, leading to misperception or misinterpretation of auditory and visual stimuli. The incidence of the psychic emergence reactions ranges from 3% to 100%. A clinically relevant range is probably 10% to 30% of adult patients who receive ketamine as a sole or major part of the anesthetic technique. Factors that affect the incidence of emergence reactions are age, dose, gender, psychological susceptibility, and concurrent drugs. Pediatric patients do not report as high an incidence of unpleasant emergence reactions as do adult patients; men also report a less frequent incidence compared with women. Larger doses and rapid administration of large doses seem to predispose patients to a frequent incidence of adverse effects. Finally, certain personality types seem prone to the development of emergence reactions. Patients who score high in psychotism on the Eysenck Personality Inventory are prone to develop emergence reactions, and individuals who commonly dream at home are more likely to have postoperative dreams in the hospital after ketamine. While numerous drugs have been used to reduce the incidence and severity of postoperative reactions to ketamine, the benzodiazepines seem to be the most effective group of drugs. Next to the undesirable psychological reactions, increasingly ketamine is described for its antidepressant effects. The dose often used for this indication is 0.5 mg/kg, given as a 40-minute infusion. This often results in a dramatic mood change within a day, often lasting for 3 to 12 days. A maintenance dose every 2 to 4 days may lengthen this effect.²⁸⁸ The precise mechanism of action of the antidepressant effects of ketamine remain unknown.

EFFECTS ON THE RESPIRATORY SYSTEM

Ketamine has minimal effects on the central respiratory drive as reflected by an unaltered response to carbon dioxide. There can be a transient (1-3 minutes) decrease in minute ventilation after the bolus administration of an induction dose of ketamine (2 mg/kg intravenously). Unusually large doses can produce apnea, but this is seldom seen. In a μ -opioid knockout mouse model, though, at supraspinal sites S(+) ketamine interacts with the μ -opioid receptor system. This interaction contributes significantly to S(+)

ketamine-induced respiratory depression and supraspinal antinociception.^{289,290} With the use of adjuvant sedatives or anesthetic drugs, respiratory depression may become clinically significant. Ketamine depresses ventilatory control in children especially with bolus doses. Ketamine is a bronchial smooth muscle relaxant. When it is given to patients with reactive airway disease and bronchospasm, pulmonary compliance is improved.

Ketamine is as effective as halothane or enflurane in preventing experimentally induced bronchospasm. The mechanism for this effect is probably a result of the sympathomimetic response to ketamine, but there are isolated bronchial smooth muscle studies showing that ketamine can directly antagonize the spasmogenic effects of carbachol and histamine. Owing to its bronchodilating effect, administration of ketamine can treat status asthmaticus unresponsive to conventional therapy. A potential respiratory problem, especially in children, is the increased salivation that follows ketamine administration, which can be modulated by an anticholinergic drug such as atropine or glycopyrrolate.

EFFECTS ON THE CARDIOVASCULAR SYSTEM

Ketamine increases arterial blood pressure, heart rate, and cardiac output in a biphasic manner. It produces a direct cardiodepressive, negative inotropic effect next to an indirect stimulatory effect due to activation of the sympathetic system. Ketamine causes the systemic release of catecholamines, inhibition of the vagal nerve, inhibition of norepinephrine reuptake at peripheral nerves and non-neuronal tissues such as the myocardium, and norepinephrine release from sympathetic ganglia.²⁹¹ Cardiodepression precedes stimulation after large-dose ketamine administration or occurs after repeated administrations when presynaptic catecholamine stores become depleted. Cardiovascular stimulation already occurs after small-dose ketamine infusion and is characterized by tachycardia, systemic and pulmonary hypertension, increases in cardiac output, and myocardial oxygen consumption. Whereas the cardiovascular stimulatory effects of ketamine generally are dominant, after termination of S-ketamine infusion, cardiovascular depression may become evident as cardiac output may decrease below pre-infusion values.²⁷³ The cardiovascular stimulatory effects of S(+) ketamine are characterized by an increase in the cardiac output of 1 L/min in the presence of 243 ng/ml S(+) ketamine.²⁷³ The cardiovascular stimulatory effect of S(+) ketamine is induced very rapidly with a half-life for onset/offset of the effect of ketamine on cardiac output of 1 to 2 minutes. The increase in hemodynamic variables is associated with increased work and myocardial oxygen consumption. The healthy heart increases oxygen supply by increased cardiac output and decreased coronary vascular resistance, so that coronary blood flow is appropriate for the increased oxygen consumption. In patients with congenital heart disease, there are no significant changes in shunt directions or fraction, or systemic oxygenation after ketamine induction of anesthesia. In patients who have increased pulmonary artery pressure (as with mitral valvular and some congenital lesions), ketamine causes a more pronounced increase in pulmonary than systemic vascular resistance. Ketamine injected directly into the CNS produces

an immediate sympathetic nervous system hemodynamic response. Ketamine also causes the sympathoneuronal release of norepinephrine, which can be detected in venous blood. Blockade of this effect is possible with barbiturates, benzodiazepines, and droperidol. The centrally mediated sympathetic responses to ketamine usually override the direct depressant effects of ketamine. Some peripheral nervous system actions of ketamine play an undetermined role in the hemodynamic effects of the drug. Ketamine inhibits intraneuronal uptake of catecholamines in a cocaine-like effect and inhibits extraneuronal norepinephrine uptake.

Stimulation of the cardiovascular system is not always desirable, and certain pharmacologic methods have been used to block the ketamine-induced tachycardia and systemic hypertension. Probably the most fruitful approach has been prior administration of benzodiazepines. Modest doses of diazepam, flunitrazepam, and midazolam all attenuate the hemodynamic effects of ketamine. It also is possible to decrease the tachycardia and hypertension caused by ketamine by using a continuous infusion technique with or without a benzodiazepine. Inhalation anesthetics and propofol blunt the hemodynamic effect of ketamine.

Uses

The many unique features of ketamine pharmacology, especially its propensity to produce unwanted emergence reactions in 10% to 20% of patients, have limited its use for routine anesthesia. Nevertheless, ketamine has an important niche in the practice of anesthesiology when its unique sympathomimetic activity and bronchodilating capabilities are indicated during induction of anesthesia. It is used for premedication, sedation, induction, and maintenance of general anesthesia. There has been increased interest in the use of ketamine in small doses for preventive analgesia, for the treatment or prevention of opiate tolerance and hyperalgesia, and in treatment of acute and chronic pain.

Induction and Maintenance of Anesthesia

The cardiovascular stimulatory effects make ketamine a desirable drug for the induction of anesthesia in unstable cardiovascular patients suffering from hypovolemia, hemorrhagic shock, or cardiovascular depression in sepsis. Ketamine bronchodilation and profound analgesia allowing the use of high oxygen concentrations make ketamine an excellent choice for induction of anesthesia in patients with reactive airway disease. Trauma patients with extensive blood loss are typical candidates for rapid-sequence anesthesia induction with ketamine. Patients with septic shock also may benefit from ketamine. The intrinsic myocardial depressant effect of ketamine may manifest in this situation if trauma or sepsis has caused depletion of catecholamine stores before the patient's arrival in the operating room. Use of ketamine in these patients does not obviate the need for appropriate preoperative preparation, including restoration of intravascular blood volume. Other cardiac diseases that can be well managed with ketamine anesthesia are cardiac tamponade and restrictive pericarditis. The finding that ketamine preserves heart rate and right atrial pressure through its sympathetic stimulating effects makes ketamine an excellent anesthetic induction and maintenance drug in this setting. Ketamine also is often used in patients with congenital heart disease, especially patients in whom the propensity

for right-to-left shunting exists. Ketamine has been successfully used in a patient susceptible to malignant hyperthermia. Ketamine combined with propofol or midazolam can be given by continuous infusion to produce satisfactory cardiac anesthesia for patients with valvular and ischemic heart disease. The combination of a benzodiazepine or of a benzodiazepine plus sufentanil with ketamine attenuates or eliminates the unwanted tachycardia and hypertension and postoperative psychological derangements. With this technique, there are minimal hemodynamic perturbations, profound analgesia, dependable amnesia, and an uneventful convalescence. The use of propofol plus small-dose ketamine also has gained increasing popularity as a total IV anesthesia technique for patients undergoing noncardiac surgery. The advantages of this combination are maintenance of stable hemodynamics and minimal ventilatory depression when allowing spontaneous ventilation.

Pain Management

Postoperative pain is a major concern of many patients and inadequately treated in as many as 30% to 50% of all postoperative patients. Multimodal analgesia combining various analgesic agents that act through different pathways is the way to manage postoperative pain. Ketamine is increasingly used as one of the constituents of this multimodal analgesia therapy. Over the years the ketamine dose used for perioperative analgesia has gradually been decreasing. Ketamine administered in small doses decreases postoperative analgesic consumption by 33%. Several meta-analyses of the use of small-dose ketamine (20 to 60 mg) perioperatively have been performed. These meta-analyses showed an overall decrease in opiate use or improved analgesia and a decrease in opiate-induced side effects, especially PONV. Side effects, especially psychomimetic effects, were minimal, especially if a benzodiazepine also was administered.

The epidural/caudal administration of ketamine (0.5 to 1 mg/kg) is effective. Although the efficacy of these doses of ketamine seems to be established, the safety of this technique has not yet received regulatory approval. The preservative of racemic mixture is potentially neurotoxic, whereas studies to date indicate preservative-free S(+) ketamine may be safe. Epidural preservative-free S(+) ketamine has been shown to be safe and of value in adjunct to corticosteroids in patients for the treatment of chronic low back pain secondary to radiculopathy.²⁹² The favorable hemodynamic effects and conservation of respiration makes intravenously and even intranasally administered ketamine useful for analgesia after extremity fractures.

The action of ketamine on opiate tolerance and hyperalgesia combined with its direct analgesic activity has led to its use in chronic pain states. Ketamine may be effective in the treatment of cancer pain, chronic peripheral and central neuropathic pain, phantom and ischemic limb pain, fibromyalgia, complex regional pain syndrome, visceral pain, and migraine. Multiple open-label studies conclude positively on the analgesic properties of ketamine in cancer pain. Randomized controlled trials, though, so far could not prove a clinical benefit of ketamine for this indication.²⁹³ Thus, while ketamine is effective for relief of postoperative pain, causing reduced opioid consumption, ketamine for most other indications appears to have limited efficacy and results in no beneficial effects.

BOX 23.3 Uses and Doses of Ketamine

Induction of general anesthesia*	0.5-2 mg/kg IV 4-6 mg/kg IM
Maintenance of general anesthesia	0.5-1 mg/kg IV with N ₂ O 50% in O ₂ 15-45 µg/kg/min IV with N ₂ O 50%-70% in O ₂ 30-90 µg/kg/min IV without N ₂ O
Sedation and analgesia	0.2-0.8 mg/kg IV over 2-3 min
Preemptive or preventive analgesia	2-4 mg/kg IM 0.15-0.25 mg/kg IV

*Lower doses are used if adjuvant drugs such as midazolam or thiopental also are given. IM, Intramuscular; IV, intravenous; N₂O, nitrous oxide.

From Reves JG, Glass P, Lubarsky DA, et al. Intravenous anesthetics. In: Miller RD, Eriksson LI, Fleischer LA, et al, eds. *Miller's Anesthesia*, 7th ed. Philadelphia: Churchill Livingstone; 2010: 719-768.

Sedation

Often, ketamine is combined with premedication of a barbiturate or benzodiazepine and an antisialagogue (e.g., glycopyrrolate) to facilitate management. The premedications reduce the dose requirement for ketamine, and the antisialagogue reduces the sometimes troublesome salivation. In adults and children, ketamine can be used as a supplement or an adjunct to regional anesthesia, extending the usefulness of the primary (local anesthetic) form of anesthesia. Also, in the emergency department ketamine is increasingly used for short painful procedures. The dose used then is between 0.1 to 0.6 mg/kg. As previously described, ketamine also may be considered for sedation of patients in a critical care unit because of its combined sedative and analgesic properties and favorable effects on hemodynamics. Ketamine can even be used safely in head injury patients when they are adequately ventilated.^{294,295}

Ketamine is particularly suitable for sedation of pediatric patients undergoing procedures outside of the operating room. Pediatric patients have fewer adverse emergence reactions than adults, and this feature makes the use of ketamine in pediatric patients more versatile.

Doses and Routes of Administration

Ketamine has been administered intravenously, intramuscularly, transcutaneously, orally, nasally, and rectally, and as a preservative-free solution epidurally or intrathecally. Most clinical use involves the IV and intramuscular (IM) routes, by which the drug rapidly achieves therapeutic concentrations. The dose depends on the desired therapeutic effect and on the route of administration. Box 23.3 contains general recommended doses for the IV and IM administration of ketamine for various therapeutic goals. Intranasal administration has an onset closer to IV administration; an oral dose of 3 to 10 mg/kg generates a sedative effect in 20 to 45 minutes. For sedation, ketamine may be given in an IM dose of 2 to 4 mg/kg. It also has been administered orally in doses of 3 to 10 mg/kg, with 6 mg/kg providing optimal conditions in 20 to 25 minutes in one study and 10 mg/kg providing sedation in 87% of children within 45 minutes in another study.

Side Effects and Contraindications

Contraindications to ketamine relate to specific pharmacologic actions and patient diseases. In patients with

increased ICP and breathing spontaneously, ketamine should be used with caution because it can increase ICP and has been reported to cause apnea. There is increasing clinical use of ketamine in emergency airway management in brain injury patients with or without other body injuries. In this setting, the current knowledge on safe management of increased ICP is continuing to grow.^{294,295}

In mechanically ventilated patients, ketamine retains the response of CBF to carbon dioxide, which makes it useful in head-injured patients because of its potential neuroprotective effect. Ketamine may be contraindicated in patients with an open eye injury or other ophthalmologic disorder, in which a ketamine induced increase in intraocular pressure would be detrimental. Because ketamine has a propensity to cause hypertension and tachycardia, with a commensurate increase in myocardial oxygen consumption, it may be contraindicated as the sole anesthetic in patients with ischemic heart disease. Likewise, it is unwise to give ketamine to patients with vascular aneurysms because of the possible sudden change in arterial blood pressure. Psychiatric disease, such as schizophrenia, and a history of adverse reaction to ketamine or one of its congeners also are contraindications. One also should consider carefully using ketamine when there is a possibility of postoperative delirium from other causes (e.g., delirium tremens, possibility of head trauma), and a ketamine-induced psychomimetic effect would confuse the differential diagnosis.

As mentioned earlier, ketamine or other NMDA receptor antagonists accentuate apoptosis in the newborn brain of animals, and the clinical implications of this are unknown. Finally, because ketamine's preservative—chlorobutanol—is neurotoxic, this formulation of ketamine for subarachnoid or epidural administration is contraindicated. S(+) ketamine is available in a preservative-free solution. The FDA has not approved the use of intrathecal or epidural ketamine. Caudal ketamine has been used for perioperative analgesia in children and neonates with 0.5 mg/kg as the optimal dose. Caudal analgesia, by combinations of ketamine and a local anesthetic, prolongs analgesia from 2.26 to 5.3 hours and reduces the need for nonopioid analgesics.²⁹⁶⁻³⁰⁰

Lastly, liver and renal toxicity occurs in the recreational abuse of ketamine. In addition, when ketamine is repeatedly administered in the treatment of chronic pain in patients with complex regional pain syndrome type 1 (CRPS), hepatotoxicity developed in patients that received two 100-hour infusions of S(+) -ketamine with a 16-day interval.^{298,301,302}

Etomidate

HISTORY

The first report on etomidate was published in 1965.³⁰³ Etomidate was introduced into clinical practice in 1972. The unique properties of etomidate include hemodynamic stability, minimal respiratory depression, cerebral protection, favorable toxicity profile, and pharmacokinetics enabling rapid recovery after either a single dose or a continuous infusion. In the 1970s, these beneficial properties led to widespread use of etomidate for induction, for maintenance of anesthesia, and for prolonged sedation in critically

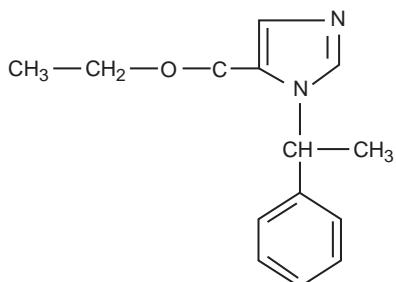


Fig. 23.16 Structure of etomidate, an imidazole derivative.

ill patients. The enthusiasm among clinicians for etomidate was tempered in the 1980s by reports that the drug can cause temporary inhibition of steroid synthesis after single doses and infusions.^{304,305} This effect, combined with other minor disadvantages (e.g., pain on injection, superficial thrombophlebitis, myoclonus, and a frequent incidence of nausea and vomiting), led to several editorials questioning the role of etomidate in modern anesthetic practice.^{306,307} Use of the drug decreased after those editorials, but its use has expanded again as a result of the rediscovery of etomidate's beneficial physiologic profile and a widening use in emergency departments and intensive care departments, combined with a lack of novel reports describing clinically significant adrenocortical suppression after induction or brief duration infusions.

PHYSICOCHEMICAL CHARACTERISTICS

Etomidate is an imidazole derivative (R-(+)-pentylethyl-1H-imidazole-5 carboxylate sulfate). Its chemical structure is illustrated in Fig. 23.16. Etomidate has a pK_a of 4.2 and is hydrophobic at physiologic pH. To increase its solubility it is formulated as a 0.2% solution either in 35% propylene glycol (Amidate; Hospira Inc., Lafe Forest, IL) or in a lipid emulsion (Etomidate-Lipuro; B. Braun, Melsungen, Germany).³⁰⁸

PHARMACOKINETICS

The pharmacokinetics of etomidate have been determined after single bolus doses and after continuous infusion. The time course of plasma disappearance after a 0.3 mg/kg bolus is shown in Fig. 23.17. The pharmacokinetics of etomidate are best described by an open three-compartment model.³⁰⁹

The drug has an initial distribution half-life of 2.7 minutes, a redistribution half-life of 29 minutes, and an elimination half-life of 2.9 to 5.3 hours.³¹⁰ Clearance of etomidate by the liver is high (18–25 mL/kg/min), with a hepatic extraction ratio of 0.5 ± 0.9 .³⁰⁹ Because redistribution is the mechanism whereby the effect after a bolus of etomidate is dissipated (Box 23.4), hepatic dysfunction should not appreciably alter recovery from a single induction dose. Etomidate is 75% protein bound.

A hemorrhagic shock model in pigs bled to a MAP of 50 mm Hg did not alter etomidate pharmacokinetics or pharmacodynamics.³¹¹ This finding contrasts with the marked changes seen in this same model with other IV anesthetics. In patients with cirrhosis, the volume of distribution is doubled, whereas clearance is normal; the result is an elimination half-life that is twice normal.³¹² The initial distribution

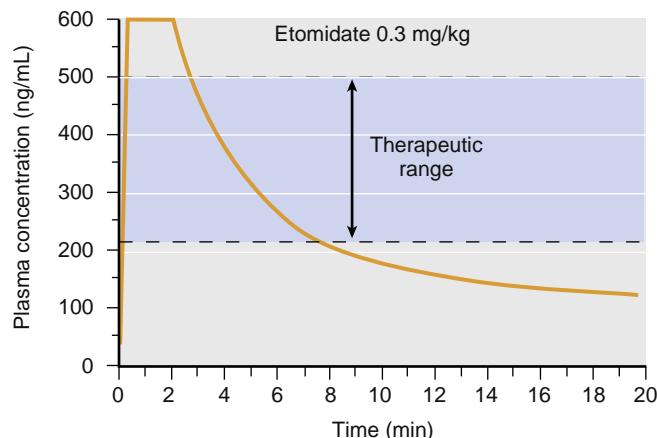


Fig. 23.17 Simulated time course of plasma levels of etomidate after an induction dose of 0.3 mg/kg. Plasma levels required for hypnosis during surgery are 300 to 500 ng/mL, with awakening usually occurring at levels less than 225 ng/mL.

BOX 23.4 Uses and Doses of Etomidate

Induction of general anesthesia	0.2–0.6 mg/kg IV
Sedation and analgesia	Limited to periods of brief sedation because of inhibition of corticosteroid synthesis

IV, Intravenous; N_2O , nitrous oxide.

From Reves JG, Glass P, Lubarsky DA, et al. Intravenous anesthetics. In Miller RD, Eriksson LI, Fleischer LA, et al, eds. *Miller's Anesthesia*, 7th ed. Philadelphia: Churchill Livingstone; 2010: 719–768.

half-life and clinical effect are likely unchanged. Increasing age is associated with a smaller initial volume of distribution and a decreased clearance of etomidate.³¹³

The short elimination half-life and the rapid clearance of etomidate make it suitable for administration in a single dose, in multiple doses, or in a continuous infusion with its context sensitive half-time being shorter than that of propofol.³¹⁴ Continuous infusion was practiced in the first decade of its clinical availability, but the now widely recognized adrenal suppression limits this application. Etomidate is metabolized in the liver primarily by ester hydrolysis to the corresponding carboxylic acid of etomidate (major metabolite) and an ethanol leaving group.³¹⁵ The main metabolite is inactive. Only 2% of the drug is excreted unchanged, the remaining part being excreted as metabolites by the kidney (85%) and bile (13%). Pathologic conditions altering serum proteins (e.g., hepatic or renal disease) affect the amount of the free (unbound) fraction and may cause a dose to have an exaggerated pharmacodynamic effect.³¹⁶

Pharmacodynamics

EFFECTS ON THE CENTRAL NERVOUS SYSTEM

The primary action of etomidate on the CNS is through the GABA_A receptor and results in hypnosis,^{317,318} which is achieved in one arm–brain circulation after a normal induction dose (0.3 mg/kg). The mechanism by which etomidate produces hypnosis is almost exclusively through

GABA_A receptor facilitation.^{318,319} This includes two effects produced by different concentrations of etomidate. The first is the positive modulation of the GABA_A receptor: activation of the receptor by agonists at concentrations associated with clinical doses. A lower dose of GABA is required in the presence of etomidate to activate the GABA_A receptor.³²⁰ The second action is called the direct activation or allosteric agonism. In supraclinical concentrations etomidate can directly, thus in absence of GABA, activate the GABA_A receptor.³²¹ These two actions suggest two independent binding sites at the GABA_A receptor.³¹⁸ These two binding sites on the $\alpha 1\beta 2\gamma 2$ GABA_A receptor contribute equally and non-cooperatively to drug interaction and gating effects. At a dose of 0.2 to 0.3 mg/kg, etomidate reduces CBF by 34% and CMRO₂ by 45% without altering MAP. CPP is maintained or increased, and there is a beneficial net increase in the cerebral oxygen supply-to-demand ratio.³²² Etomidate, given in doses sufficient to produce EEG burst suppression, acutely decreases ICP by 50% in patients with already increased ICP, returning increased ICP to almost normal values.³²³ The decrease in ICP is maintained in the period immediately after intubation. To maintain the effects of etomidate on ICP, high infusion rates (60 μ g/kg/min) are necessary. Controversy remains on the neuroprotective qualities of etomidate. There is a dose-dependent increase in latency and a decreasing amplitude of the auditory evoked potentials.³²⁴

Preliminary animal experiments suggest that in a case of acute fetal distress and hypoxic injury propofol and midazolam may be preferred over etomidate to protect the fetal brain as the first choice anesthetic in cesarean delivery.^{199,325,326} Etomidate has been associated with grand mal seizures and produces increased EEG activity in epileptogenic foci. This feature has proven useful for intraoperative mapping of seizure foci before surgical ablation.^{327,328} BIS monitor values decrease after etomidate bolus administration and return to baseline during recovery.³²⁹ During etomidate infusion, the BIS values reliably predict the depth of sedation and hypnosis.³³⁰

Effects on the Respiratory System

Etomidate has less effect on ventilation than other anesthetics used to induce anesthesia. It does not induce histamine release in healthy patients or in patients with reactive airway disease.³³¹ Ventilatory response to carbon dioxide is depressed by etomidate, but the ventilatory drive at any given carbon dioxide tension is greater than that following an equipotent dose of methohexitol.¹⁵³ Induction with etomidate produces a brief period of hyperventilation, sometimes followed by a similarly brief period of apnea,³³² which results in a slight ($\pm 15\%$) increase in PaCO₂, but no change in the partial pressure of arterial oxygen (PaO₂).³³³ Etomidate's action on pulmonary vascular tone is similar to the actions observed with ketamine and propofol; that is, they attenuate the vasorelaxant responses to acetylcholine and bradykinine.³³⁴

Effects on the Cardiovascular System

The hemodynamic stability seen with etomidate is due to its lack of effect on the sympathetic nervous system and on the function of the baroreceptor. The effect of etomidate on the $\alpha 2$ -adrenoceptors generates an increase in blood

pressure in vivo; this may contribute to the cardiovascular stability after induction of anesthesia. The minimal effect of etomidate on cardiovascular function sets it apart from other rapid-onset anesthetics.^{335,336} Etomidate has proven useful in patients with valvular or ischemic heart disease undergoing noncardiac surgery and in patients with poor cardiac function.^{337,338} In patients receiving etomidate during induction of anesthesia, more hypertension and tachycardia occurs after etomidate compared to propofol.³³⁹ The myocardial oxygen supply-to-demand ratio is well maintained.³⁴⁰ Etomidate lacks analgesic efficacy, however, and needs to be combined with an opiate to prevent hemodynamic perturbations during laryngoscopy and intubation.

In the setting of a hemorrhagic shock, etomidate provides advantages for induction of anesthesia. In contrast to other drugs, in a pig model of hemorrhagic shock the pharmacodynamics and pharmacokinetics of etomidate were minimally altered.³¹¹

Endocrine Effects

In 1983 Ledingham and Watt reported retrospective data showing increased mortality among intensive care patients receiving long-term etomidate infusion compared to patients receiving benzodiazepines.³⁰⁴ They postulated that adrenal cortical suppression could be the cause of this increased mortality.

Soon after this publication, clinical investigators confirmed the adrenocortical suppression by etomidate.^{305,341}

The specific endocrine effects manifested by etomidate are a dose-dependent reversible inhibition of the enzyme 11 β -hydroxylase, which results in decreased biosynthesis of cortisol. The blockade of the cytochrome P450-dependent enzyme 11 β -hydroxylase also results in decreased mineralocorticoid production and an increased formation of intermediaries (11-deoxycorticosterone) (Fig. 23.18). Subsequent research showed that etomidate is far more potent as an inhibitor of steroid synthesis than as a sedative hypnotic agent.^{341,342} The etomidate concentrations associated with adrenal cortical suppression are less than 10 ng/mL, which are much lower than the concentrations needed for hypnosis (more than 200 ng/mL). The disparate concentrations for hypnosis and adrenotoxicity may explain the dramatic difference in duration of these two actions.⁵⁷

The concerns about the use of etomidate and etomidate-induced adrenal toxicity in critically ill patients is still a matter of strong debate in the critical care community. A Cochrane review in 2015 of single-dose etomidate versus other induction agents for endotracheal intubation in critically ill patients reveals no conclusive evidence that etomidate increases mortality.³⁴³ As indicated earlier, etomidate is associated with suppression of adrenal steroidogenesis, which can last up to 72 hours. However, the clinical impact of this adrenal suppressive effect is not certain.³⁴⁴

The Corticosteroid Therapy of Septic Shock (CORTICUS) study followed 500 patients with septic shock, who were randomized to receive either low-dose corticosteroid therapy or placebo. Twenty percent of the patients received etomidate. The study concluded that there was no benefit of low-dose corticosteroid therapy to long-term outcome.³⁴⁵ Retrospective analyses of the CORTICUS population suggest that patients receiving etomidate before enrollment

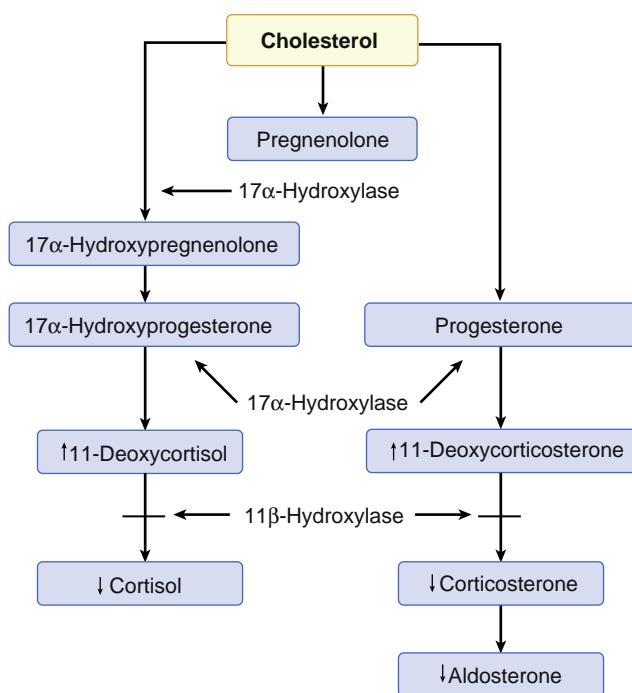


Fig. 23.18 Pathway for the biosynthesis of cortisol and aldosterone. The sites at which etomidate affects cortisol-aldosterone synthesis by its action on 11 β -hydroxylase (major site) and 17 α -hydroxylase (minor site) are illustrated.

had a 28-day mortality significantly higher and that steroid supplements provided no benefit.^{346,347} Other studies designed to evaluate the effect of etomidate on morbidity and mortality and hospital and ICU length of stay are not conclusive.³⁴⁸⁻³⁵¹ In conclusion, the impact of the use of a single dose of etomidate in critically ill patients remains unclear.

Uses

INDUCTION OF ANESTHESIA

The induction dose of etomidate is 0.2 to 0.6 mg/kg.³⁵² The induction dose is reduced by premedication with an opiate, a benzodiazepine, or a barbiturate. Onset of anesthesia after a routine induction dose of 0.3 mg/kg of etomidate is rapid (one arm–brain circulation). Various infusion schemes have been devised to use etomidate as a maintenance anesthetic for the hypnotic component of anesthesia in the past. After the publications on the adrenocortical suppressive effects of etomidate, continuous infusion has been abandoned.

Etomidate is most appropriate in patients with cardiovascular disease, reactive airway disease, intracranial hypertension, or any combination of disorders indicating the need for an induction agent with limited or beneficial physiologic side effects. The hemodynamic stability of etomidate is unique among the rapid onset anesthetics used to induce anesthesia. In multiple studies, etomidate has been used for induction in patients with a compromised cardiovascular system who are undergoing coronary artery bypass surgery or valve surgery, and in patients requiring induction of general anesthesia for percutaneous transluminal

coronary angioplasty, aortic aneurysm repair, and thoracic surgery. For cardioversion, the rapid onset, quick recovery, and maintenance of arterial blood pressure in these sometimes hemodynamically tenuous patients, combined with continued spontaneous respiration, make etomidate an acceptable choice.³⁵³ Etomidate has been successfully used in neurosurgical procedures such as giant aneurysm clippings, making it a reasonable choice during neurosurgical induction.³⁵⁴ In addition, etomidate should be considered as an anesthetic induction agent to reduce increased ICP when maintenance of cerebral or coronary perfusion pressure is also important.

Trauma patients with questionable intravascular volume status may be well served by an induction of anesthesia with etomidate. When using etomidate in trauma patients, loss of consciousness by itself can be associated with decreased adrenergic output, and controlled ventilation can exacerbate the cardiovascular effects of a decreased preload. Both of these factors may cause a significant decrease in arterial blood pressure during induction of anesthesia despite etomidate having no direct cardiovascular drug effect.

Short-term sedation with etomidate is useful in hemodynamically unstable patients, such as patients requiring cardioversion or patients requiring sedation after an acute myocardial infarction or with unstable angina for a minor operative procedure.³⁵³ When used during electroconvulsive therapy, etomidate can produce longer seizures compared with other hypnotics.^{355,356} Induction of anesthesia with etomidate is an independent risk factor in the development of an emergence delirium.³⁵⁷

Treatment in Hypercortisolism

Etomidate has a special place in the treatment of endogenous hypercortisolism. It is proven to be an effective parenteral treatment for this indication. In patients with unstable hemodynamics, patients with a sepsis, or patients with a psychosis, treatment should be performed under intensive care conditions.³⁵⁸

Side Effects

Although etomidate provides stable hemodynamics and minimal respiratory depression, it is associated with several adverse effects when used for induction, including PONV, pain on injection, myoclonic movement, and hiccups. More recently, etomidate in a lipid emulsion was associated with an equal or an increased incidence of postoperative nausea compared with propofol.³⁵⁹⁻³⁶¹

The lipid formulation of etomidate is associated with a much less frequent incidence of pain on injection, thrombophlebitis, and histamine release.^{362,363} Pain on injection may be reduced by injecting lidocaine, 20 to 40 mg immediately before injection of etomidate.

The incidence of muscle movement (myoclonus) and of hiccups is highly variable (0%-70%), but myoclonus is reduced by premedication with a hypnotic like midazolam or a small dose of magnesium 60 to 90 seconds before the induction dose of etomidate is given.^{364,365}

Novel Etomidate Derivatives

Etomidate is a well-known and widely used anesthetic for induction of anesthesia. The limitations of etomidate are, as

mentioned earlier, adrenocortical suppression, myoclonus, and PONV. Modifying etomidate could improve its clinical utility and produce etomidate derivatives with a better profile. Methoxycarbonyl etomidate (MOC) is an etomidate derivative and is rapidly metabolized to methoxycarbonyl etomidate carboxylic acid (MOC-ECA). MOC has almost equal hypnotic potency as etomidate, and the duration of the induced anesthesia is short due to rapid metabolism by nonspecific esterase enzymes. In preclinical studies MOC may not act as an inhibitor of adrenal steroid synthesis.³⁶⁶ The accumulation of metabolites, leading to delayed recovery, makes it less than ideal for infusion.

Carboetomidate, another derivative, contains a five-membered pyrrole ring instead of an imidazole. In tadpoles and rats, carboetomidate reduces the adrenal suppression potency by three orders. Carboetomidate has potent hypnotic properties by activating GABA_A receptors, which causes minimal hemodynamic changes.³⁶⁷ Another potential benefit is its inhibition of the 5-HT3 receptor in a rat model; carboetomidate may have decreased emetogenic properties.

Another etomidate derivative, methoxycarbonyl-carboetomidate (MOC-carboetomidate), combines the favorable effects with no adrenal suppression and potency of the parent compound, but has a longer duration of action and makes it disadvantageous for longer infusions.

Cyclopropyl-methoxycarbonyl metomidate (CPMM) and dimethyl-methoxycarbonyl metomidate (DMMM) are the newest derivatives of etomidate. They have a higher potency and fast recovery time after infusion duration of 2 hours. So far, they are most promising in animal studies and inflammatory sepsis models.

Dexmedetomidine

HISTORY

The α_2 -adrenergic receptor agonists have sedative, anxiolytic, hypnotic, analgesic, and sympatholytic effects. Its potential for use in anesthesia was recognized in patients who were treated with clonidine.³⁶⁸ Soon a reduction of the minimum alveolar concentration (MAC) of halothane by clonidine was described.³⁶⁹ Dexmedetomidine is a more selective α_2 -agonist with a selectivity ratio for the α_2 -receptor compared with the α_1 -receptor of 1600:1, as compared to a ratio of 220:1 for clonidine. It was introduced in clinical practice in the United States in 1999 and approved by the FDA only as a short-term (<24 hours) sedative for mechanically ventilated adult ICU patients. Dexmedetomidine is used for prolonged sedation and anxiolysis in the ICU, as well as outside of the ICU in various settings, including sedation and adjunct analgesia in the operating room, sedation in diagnostic and procedure units, and for other applications such as withdrawal/detoxification amelioration in adult and pediatric patients.^{370,371}

PHYSICOCHEMICAL CHARACTERISTICS

Dexmedetomidine is the S-enantiomer of medetomidine, a substance that has been used for sedation and analgesia in veterinary medicine for many years.³⁷² It shows a high ratio of specificity for the α_2 -receptor ($\alpha_2/\alpha_1 = 1600:1$) compared

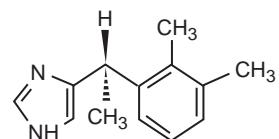


Fig. 23.19 Chemical structure of dexmedetomidine.

with clonidine ($\alpha_2/\alpha_1 = 220:1$), making it a complete α_2 -agonist.³⁷³ The pK_a is 7.1. Dexmedetomidine belongs to the imidazole subclass of α_2 -receptor agonists, similar to clonidine, and its structure is illustrated in Fig. 23.19. It is freely soluble in water and available as a clear isotonic solution containing 100 μg per mL and 9 mg sodium chloride per mL of water. Before infusion, this solution is diluted to a concentration of 4 $\mu\text{g}/\text{mL}$ or 8 $\mu\text{g}/\text{mL}$ by adding either saline, 5% glucose, mannitol, or Ringer lactate solution. It is not to be combined with amfoteracine B, amfoteracine B in liposomes, diazepam, phenytoin, gemtuzumab, irinotecan, or pantoprazole.

METABOLISM AND PHARMACOKINETICS

Dexmedetomidine undergoes almost complete biotransformation with very little unchanged dexmedetomidine excreted in urine and feces. Biotransformation involves both direct glucuronidation as well as cytochrome P450-mediated metabolism. The major metabolic pathways of dexmedetomidine are: direct N-glucuronidation to inactive metabolites, hydroxylation (mediated primarily by CYP2A6), and N-methylation. Polymorphism in CYP2A6 does not influence clinical dosing regimens.³⁷⁴ Dexmedetomidine is 94% protein bound, and its concentration ratio between whole blood and plasma is 0.66. Dexmedetomidine has effects on cardiovascular variables, potentially causing bradycardia, transient hypertension or hypotension, and may alter its own pharmacokinetics. With large doses, there is marked vasoconstriction, which probably reduces the drug's volumes of distribution. The observed hypertension may be avoided by decreasing the loading dose or by increasing the time of administration.

In essence, dexmedetomidine displays nonlinear pharmacokinetics.³⁷⁵ Its pharmacokinetics in volunteers are best described by a three-compartment model (see Table 23.1). Many subsequent studies in various patient populations have investigated the clinical pharmacokinetics and pharmacodynamics, the results of which are reviewed and summarized by Weerink and colleagues.³⁷⁶ One of the findings is that the bodyweight adjustment dosing that is currently applied is only justified in a non-obese population. For obese patients, fat-free mass may be more appropriate, but this is still subject to investigation.

In subjects with varying degrees of hepatic impairment (Child-Pugh Class A, B, or C), clearance values for dexmedetomidine are slower than in healthy subjects. The mean clearance values for patients with mild, moderate, and severe hepatic impairment are 74%, 64%, and 53% of those observed in the normal healthy subjects, respectively.

The pharmacokinetics of dexmedetomidine are not influenced by renal impairment (creatinine clearance <30 mL/min) or age. In patients with severe renal disease, the sedative effect may be stronger, due to a lower

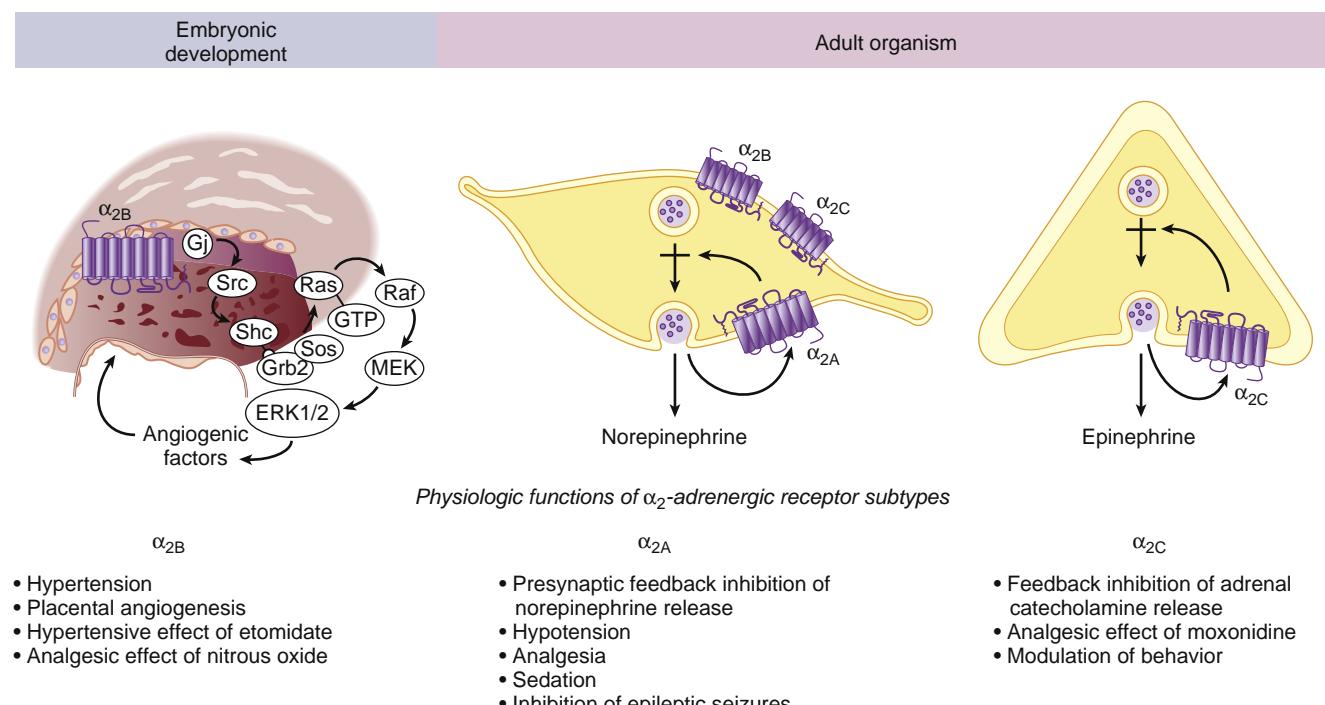


Fig. 23.20 The different physiologic functions of α_2 adrenoreceptors. The top panel depicts the three α_2 receptor subtypes acting as presynaptic inhibitory feedback receptors to control the release of norepinephrine and epinephrine from peripheral or central adult neurons. Also, a negative feedback loop has been seen in the adrenal gland. Alpha2B receptors have been involved in the development of the placental vascular system during prenatal development. The lower panel lists a series of physiologic effects with its associated α_2 adrenoreceptors. (From Paris A, Tonner PH. Dexmedetomidine in anaesthesia. *Curr Opin Anaesthesiol*. 2005;18:412-418.)

degree of plasma protein binding. Clearance is a function of height.^{375,377} The elimination half-life of dexmedetomidine is 2 to 3 hours, with a context-sensitive half-time ranging from 4 minutes after a 10-minute infusion to 250 minutes after an 8-hour infusion. Postoperative patients sedated with dexmedetomidine display similar pharmacokinetics to the pharmacokinetics seen in volunteers.³⁷⁸ No clinically relevant cytochrome P450-mediated drug interaction has been found.

PHARMACOLOGY

Dexmedetomidine acts as a nonselective α_2 -agonist on membrane bound G-protein coupled α_2 -adrenoreceptors. Intracellular pathways include inhibition of adenylate cyclase and modulation of calcium and potassium ion channels. Three subtypes of α_2 adrenoreceptors have been described in humans: α_2A , α_2B , and α_2C (Fig. 23.20).³⁷⁹ The α_2A adrenoreceptors are primarily distributed in the periphery, whereas α_2B and α_2C are in the brain and spinal cord. Postsynaptically located α_2 adrenoreceptors in peripheral blood vessels produce vasoconstriction, whereas presynaptic α_2 adrenoreceptors inhibit the release of norepinephrine, potentially attenuating the vasoconstriction. The overall response to α_2 adrenoreceptor agonists is related to the stimulation of α_2 adrenoreceptors located in the CNS and spinal cord. These receptors are involved in the sympatholysis, sedation, and antinociceptive effects of α_2 adrenoreceptors.³⁸⁰ The α_2 agonists have the advantage that their effects are readily reversible by α_2 -adrenergic antagonists (e.g., atipamezole).³⁸¹ Atipamezole is currently not approved for use in humans.

Effects on the Central Nervous System

SEDATION

The α_2 agonists produce their sedative-hypnotic effect by an action on α_2 receptors in the locus caeruleus and an analgesic action at α_2 receptors within the locus caeruleus and within the spinal cord.³⁸² Dexmedetomidine produces a decrease in activity of the projections of the locus caeruleus to the ventrolateral preoptic nucleus. As a result GABAergic and galanin release in the tuberomammillary nucleus is increased, producing a decrease in histamine release in cortical and subcortical projections.³⁸³ The α_2 agonists inhibit ion conductance through L-type or P-type calcium channels and facilitate conductance through voltage-gated calcium-activated potassium channels. Dexmedetomidine induces sedation through different receptors than the sedative drugs propofol or benzodiazepines, which exert their action through the GABA system. The sedative effect of dexmedetomidine acts through the endogenous sleep-promoting pathways, generating natural sleep patterns (Fig. 23.21).³⁸⁴ Patients have been described as being very easy to wake up and having the ability to follow commands and cooperate while being tracheally intubated. Undisturbed, patients were noted to fall asleep momentarily.³⁸⁵ This characteristic allows for “daily wake up” tests to be done in a safe fashion. This critical test—when ventilated ICU patients are taken off all sedatives to assess their mental status and titrate sedation—shortens their ventilated and ICU length of stay.^{386,387} The plasma concentration at which significant yet reusable sedation is achieved is about

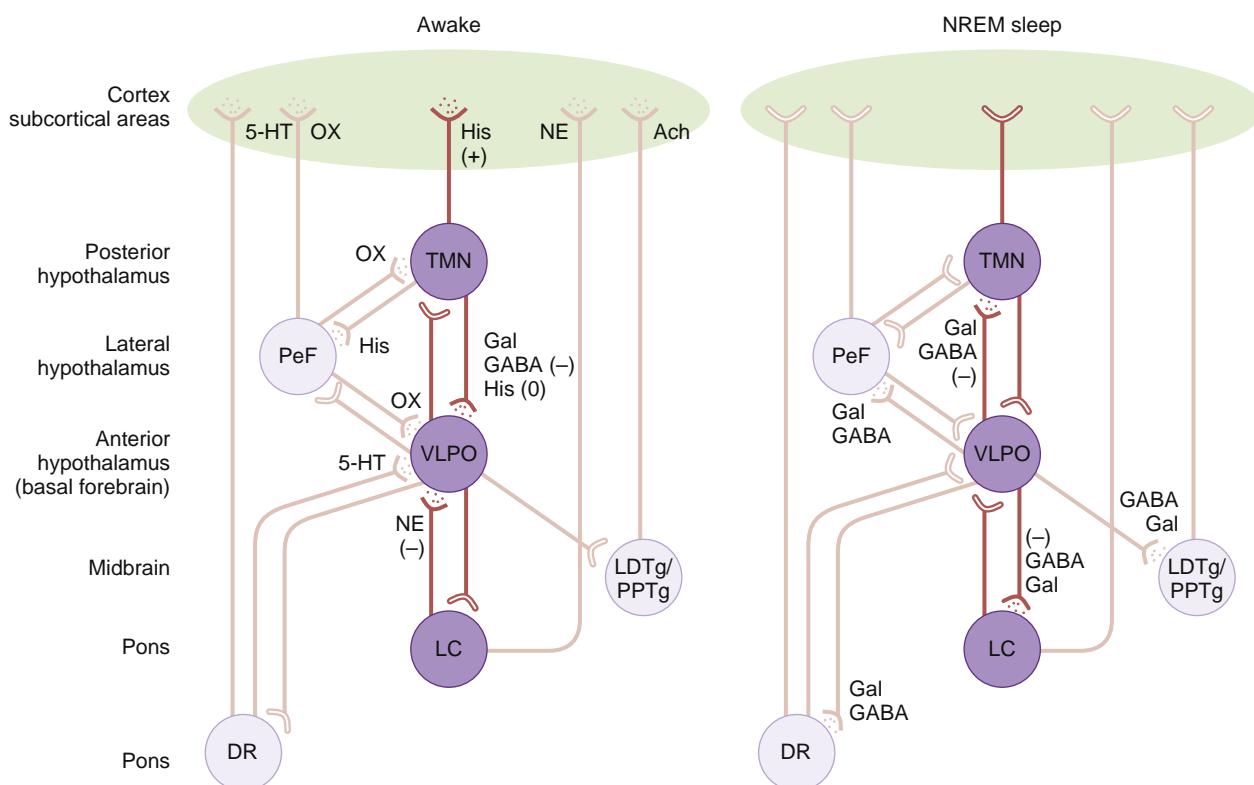


Fig. 23.21 Dexmedetomidine has been shown to induce a non–rapid eye movement sleeping pattern (NREM). The stimulation of the locus caeruleus (LC) by dexmedetomidine (right diagram) releases the inhibition the LC has over the ventrolateral preoptic nucleus (VLPO). The VLPO subsequently releases γ -aminobutyric acid (GABA) onto the tuberomammillary nucleus (TMN). This inhibits the release of the arousal-promoting histamine on the cortex and forebrain, inducing the loss of consciousness. (From Ebert T, Maze M. Dexmedetomidine: another arrow for the clinician's quiver. *Anesthesiology*. 2004;101:569–570.)

0.2 to 0.3 ng/mL. Unarousable deep sedation is thought to occur at plasma concentrations above 1.9 ng/mL.³⁸⁸

The number of patients experiencing delirium in the ICU is significantly lower when sedated with dexmedetomidine, compared to propofol or lorazepam,³⁸⁹ or midazolam.³⁹⁰

Although the precise mechanism by which dexmedetomidine preserves cognition is still unclear, there are data that suggest that the suppression of α_5 γ -aminobutyric acid type A receptor expression after exposition to an anesthetic may play a role.³⁹¹

ANALGESIA

The analgesic effect of the α_2 agonists is mediated through stimulation of the α_{2C} and α_{2A} receptor in the dorsal horn, directly suppressing pain transmission by reducing the release of pronociceptive transmitters, substance P and glutamate, and hyperpolarization of interneurons.³⁹² Systemic use of dexmedetomidine has an opioid sparing effect during surgery and postoperatively.³⁹³ This is advantageous in patients who are prone to postoperative apnea or hypoventilation, as with patients undergoing bariatric surgery.³⁹⁴ In the postoperative ICU setting, narcotic requirements are reduced by 50% when patients are receiving a dexmedetomidine drip compared with placebo.³⁸⁵ During general anesthesia, it reduces the MAC of inhaled anesthetics.^{395,396}

Like clonidine, dexmedetomidine is frequently used as an adjuvant in central or peripheral neural blockade. When administered caudally, 1 μ g/kg as adjuvant to bupivacaine 0.25% 1 mL/kg, in children undergoing inguinal hernia

repair, response to hernial sac traction is reduced and postoperative analgesia is prolonged.³⁹⁷ Dexmedetomidine has been investigated in volunteers when administered as an adjuvant to ropivacaine in ulnar nerve block³⁹⁸ and tibial nerve block.³⁹⁹ Both studies showed intensification and foremost prolongation of the sensory blockade. This effect is likely elicited by prolonged hyperpolarization of the unmyelinated C-fibers (sensory), and to a lesser extent of the A-fibers (motor function).

Central Nervous System Protection and Other Central Nervous System Effects

The CNS protective effects are not well defined. Dexmedetomidine in animal models of incomplete cerebral ischemia and reperfusion reduces cerebral necrosis and improves neurologic outcome. The prevalent idea is that dexmedetomidine reduces the intracerebral catecholamine outflow during injury. The neuroprotection may be attributed to modulation of proapoptotic and antiapoptotic proteins.⁴⁰⁰ Also, the reduction of the excitatory neurotransmitter glutamate during injury may explain some of the protective effects.⁴⁰¹

In patients undergoing transsphenoidal hypophysectomy, dexmedetomidine has no effect on lumbar cerebral fluid pressure.⁴⁰² In other studies, CBF velocity at the middle cerebral artery, as measured by transcranial Doppler,

decreased with increasing concentrations of dexmedetomidine but CO_2 responsiveness and autoregulation were preserved.^{403,404} The decrease in CBF is not accompanied by a reduction in CRMO_2 . More recently, in a study in six normal volunteers, the administration of dexmedetomidine to achieve serum levels of 0.6 ng/mL and 1.2 ng/mL (with and without hyperventilation) produced the predicted reduction of CBF with a concomitant reduction in CRMO_2 .⁴⁰⁵ This finding suggests that on the maintenance of the cerebral oxygen supply-to-demand relationship, further work in injured brains needs to be done.

Dexmedetomidine has been used in neurosurgical procedures involving neurophysiologic monitoring. Cortical evoked potentials, amplitudes, and latencies were minimally affected when using dexmedetomidine intraoperatively. It may also be suitable as an anesthetic adjunct during seizure surgery, since the epileptiform activity of seizure foci was not reduced by dexmedetomidine.⁴⁰⁶

EFFECTS ON THE RESPIRATORY SYSTEM

In spontaneous breathing volunteers, dexmedetomidine at concentrations producing significant sedation reduces minute ventilation, but results in no change in

arterial oxygenation, pH, or the slope in the CO_2 ventilatory response curve. In a study comparing the effects of remifentanil and dexmedetomidine on respiratory parameters in normal volunteers, the hypercapnic ventilatory response was unaffected even at doses that produced unresponsiveness to vigorous stimulation.⁴⁰⁷ Dexmedetomidine exhibited a hypercarbic arousal phenomenon, which has been described during normal sleep.

EFFECTS ON THE CARDIOVASCULAR SYSTEM

Ebert and colleagues performed a study in volunteers using a target-controlled infusion system to provide increasing concentrations (0.7 to 15 ng/mL) of dexmedetomidine (Fig. 23.22). The lowest two concentrations produced a decrease in MAP (13%) followed by progressive increase (12%). Increasing concentrations of dexmedetomidine also produce progressive decreases in heart rate (maximum 29%) and cardiac output (35%). The most commonly reported hemodynamic adverse reactions associated with dexmedetomidine in a phase III trial in 401 patients were hypotension (30%), hypertension (12%), and bradycardia (9%).³⁷² The initial increase in arterial blood pressure is probably due to the vasoconstrictive effects of dexmedetomidine

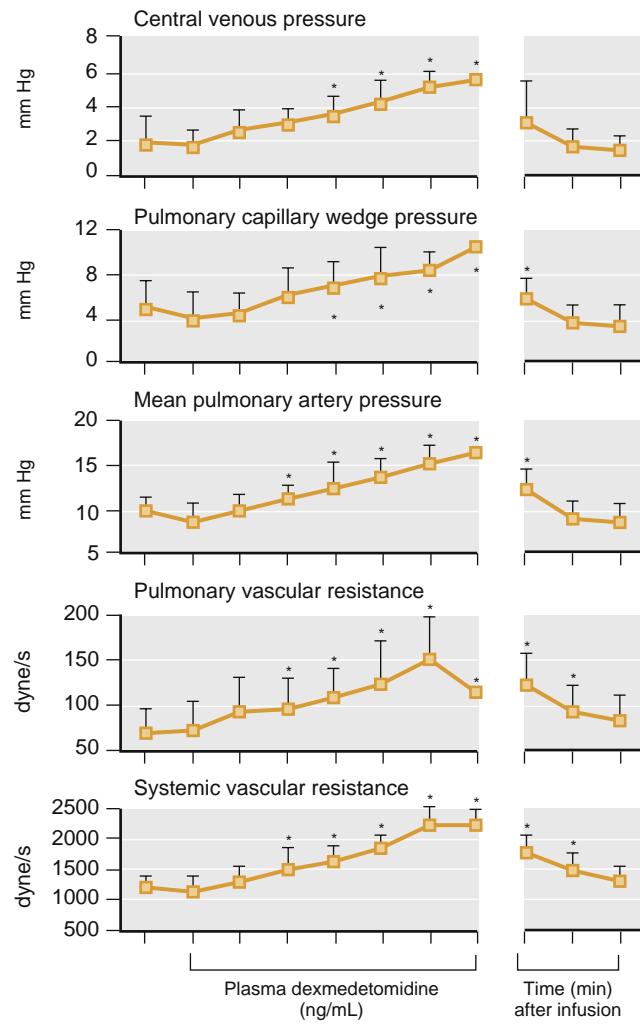
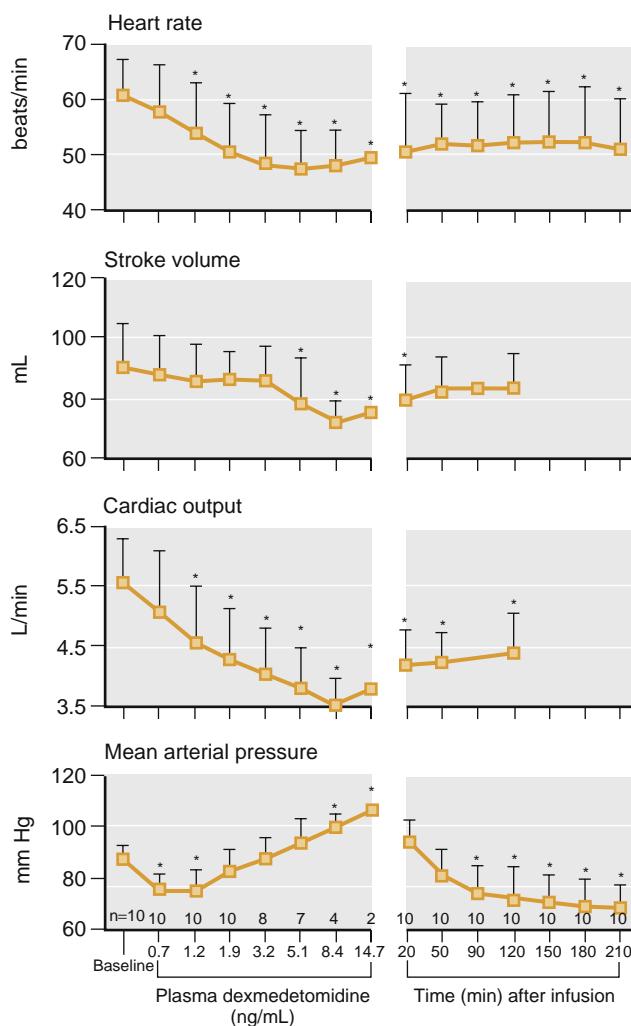


Fig. 23.22 Effects of increasing plasma concentrations of dexmedetomidine.

when stimulating peripheral α_2 receptors. The incidence of hypotension and bradycardia may be related to the administration of a large intravenous “loading” dose. Omitting the loading dose or not giving more than 0.4 $\mu\text{g}/\text{kg}$ reduces the incidence of hypotension or makes it less pronounced. Giving the loading dose over 20 minutes also minimizes the transient hypertension.⁴⁰⁸ In several studies after IM and IV administration, dexmedetomidine caused, in a small percentage of patients, profound bradycardia (<40 beats/min) and occasionally sinus arrest/pause. Generally, these episodes resolved spontaneously or were readily treated without adverse outcome by anticholinergics. No rebound effects have been found when discontinuing a dexmedetomidine infusion, even when it was given for more than 24 hours.⁴⁰⁹ As clonidine and dexmedetomidine have shown to reduce perioperative oxygen consumption and blunt the sympathetic response to surgery, cardiac outcome may be improved.^{410,411} However, more studies are needed to determine whether dexmedetomidine is beneficial in decreasing the risk of myocardial ischemia.

USES

Dexmedetomidine has been approved as a short-term sedative for adult intubated patients in the ICU. Given its well-documented beneficial effects of anxiolysis, sedation, analgesia, and sympatholysis with minimal respiratory depression, it also has been used in various other clinical scenarios. It is registered for use as a sedative during radiological or invasive procedures. Two studies, comprising 140 children 1 to 7 years old, reported successful sedation for MRI scans compared with midazolam or propofol.⁴¹² For a thorough review of a wide range of studies on various procedures under sedation in different populations, we refer to Gerlach et al.⁴¹³

As a premedicant, dexmedetomidine, at IV doses of 0.33 to 0.67 $\mu\text{g}/\text{kg}$ given 15 minutes before surgery, seems efficacious, while minimizing the cardiovascular side effects of hypotension and bradycardia.³⁹⁶ Dexmedetomidine has a high bioavailability when administered nasally or buccally. This improves compliance and absorption in younger children. A dose of 3 to 4 $\mu\text{g}/\text{kg}$ 1 hour before surgery is safe and effective.

In a study comparing the efficacy of dexmedetomidine or propofol as a sedative agent in a group of 40 patients receiving local anesthesia or regional blocks, dexmedetomidine (1 $\mu\text{g}/\text{kg}$ given over 10 minutes) when used for intraoperative sedation resulted in a slower onset than propofol (75 $\mu\text{g}/\text{kg}/\text{min}$ for 10 minutes) but had similar cardiorespiratory effects when titrated to equal sedation. The average infusion rate of dexmedetomidine intraoperatively to maintain a BIS value of 70 to 80 was 0.7 $\mu\text{g}/\text{kg}/\text{min}$. Sedation was more prolonged after termination of the infusion, as was recovery of arterial blood pressure. Dexmedetomidine can also produce profound sedation, and it has been used as a total IV anesthetic when given at 10 times the normal sedation concentration range.⁴¹⁴ This characteristic, combined with the cooperative status of the patient at a lighter sedative level, and its analgesic effect with sparing of respiratory function, makes the drug suitable as a hypnotic during surgical procedures like awake craniotomy, deep brain stimulation, surgery near speech areas, or awake carotid endarterectomies, with fewer

fluctuations from the desired sedation level and more stable hemodynamics.⁴⁰³ A recent study shows that dexmedetomidine may be advantageous by improving the quality of emergence from general anaesthesia in avoiding coughing, agitation, hypertension, tachycardia, and shivering. This may be achieved by administration of dexmedetomidine 1 $\mu\text{g}/\text{kg}$ intravenously at the end of surgery. Time to extubation is not prolonged.⁴¹⁵ The opioid-sparing effects are advantageous in the performance of bariatric surgery in patients who are prone to postoperative respiratory depression.³⁹⁴

Dexmedetomidine can be employed for addiction treatment; it has been described for use in rapid opioid detoxification, cocaine withdrawal, and iatrogenic-induced benzodiazepine and opioid tolerance after prolonged sedation.⁴¹⁶ The use in opioid/benzodiazepine withdrawal therapy in pediatric patients during mechanical ventilation in intensive care areas has been described as well.⁴¹⁷

Dexmedetomidine may produce dry mouth due to a decrease in salivation. Combined with the sparing effect on respiratory function, this effect is beneficial for the facilitation of awake fiberoptic intubation, an application which is rapidly emerging.⁴¹⁸ Furthermore, dexmedetomidine decreases intraocular pressure and decreases the shivering threshold.⁴¹⁹

The role of general anaesthesia in oncological surgery is still under debate. Studies of the *in vitro* and *in vivo* effects on lung carcinoma and neuroglioma cell lines have shown that dexmedetomidine enhanced cancer proliferation and migration, primarily by the upregulation of anti-apoptotic proteins. The clinical relevance of these findings remains to be determined.^{163a}

INTENSIVE CARE UNIT

Dexmedetomidine may have advantages over propofol for sedation in mechanically ventilated postoperative patients. Heart rate was slower in the dexmedetomidine group, whereas MAP was similar. The $\text{PaO}_2/\text{FiO}_2$ ratio was significantly higher in the dexmedetomidine group. Time to extubation of the trachea after discontinuation of the infusion was similar at 28 minutes. Patients receiving dexmedetomidine had greater recall of their stay in the ICU, but all described this as pleasant overall.⁴²¹ Several other studies have confirmed the decreased requirement for opioids (>50%) when dexmedetomidine is used for sedation compared with propofol or benzodiazepines. Hemodynamics during weaning are more stable, which benefits patients with high risk for myocardial ischemia.⁴²² For sedation in the ICU, loading doses of 0.5 to 1 $\mu\text{g}/\text{kg}$ have been used. Omitting the bolus dose or giving the lower dose has been associated with fewer episodes of severe bradycardia and other hemodynamic perturbations. Infusion rates of 0.1 to 1 $\mu\text{g}/\text{kg}/\text{h}$ are generally needed to maintain adequate sedation. Delirium in the ICU is a risk factor for increased length of stay and increased mortality.⁴²³ In a double-blind, randomized controlled trial of sedation in ventilated patients with dexmedetomidine versus lorazepam, it was found that using dexmedetomidine infusions provided more days alive without delirium or coma and a greater amount of time spent at the appropriate sedation level compared with lorazepam.³⁸⁹ It also improved the patient's ability to communicate pain, compared to midazolam or propofol in two

recent trials.³⁸⁶ The unique characteristics of dexmedetomidine, that is providing adequate sedation with minimal respiratory depression, make this selective α_2 -adrenoceptor agonist very useful when weaning patients from the ventilator.⁴²⁴ While the FDA approved the use of dexmedetomidine infusions for 24 hours or less, multiple studies have shown the safety of using this agent for longer periods, even up to 30 days.³⁹⁰

Droperidol

HISTORY

Janssen^{298,301} synthesized haloperidol, the first member of the butyrophenones, which became the primary neuroleptic component in neuroleptanesthesia. In 1959, DeCastro and Mundeleer combined haloperidol with phenoperidine (a meperidine derivative also synthesized by Janssen) in the forerunner to the practice of neuroleptanesthesia. Droperidol, a derivative of haloperidol, and fentanyl (a phenoperidine congener), both synthesized by Janssen, were used by DeCastro and Mundeleer in a combination they reported to be superior to haloperidol and phenoperidine. This neuroleptanesthesia combination produced more rapid onset of analgesia, less respiratory depression, and fewer extrapyramidal side effects. The fixed combination of droperidol and fentanyl, marketed as Innovar in the United States, was the drug primarily used for neuroleptanesthesia. The use of neuroleptanesthesia has largely disappeared in modern anesthetic practice. The primary use of droperidol in anesthesia has been as an antiemetic and to a lesser extent as a sedative and antipruritic. In addition, droperidol is used as an antipsychotic agent and to reduce agitation.⁴²⁵

In 2001, the FDA issued a black box warning regarding the use of droperidol and its potential for fatal arrhythmias and recommended that it be administered only during continuous electrocardiogram monitoring. With the withdrawal of droperidol in certain countries and more stringent labeling regarding potentially lethal dysrhythmias in others, the use of droperidol has decreased markedly. The validity of the risk of low-dose droperidol in causing QT prolongation, dysrhythmias, and death has been challenged by numerous editorials, articles, and letters reviewing the cases that prompted this action.^{298,426-430} In Europe, 19 out of 25 countries with council members in the European Society of Anesthesiologists reported that droperidol is regularly used in a dosage of 0.5 to 2.5 mg for the prevention of PONV. Furthermore, in 2007, an international consensus panel recommended droperidol despite the FDA warning as a first-line antiemetic.^{298,431}

Droperidol is a butyrophenone, a fluorinated derivative of phenothiazines (Fig. 23.23). Butyrophenones produce CNS depression, characterized by marked apparent tranquility

and cataleptic immobility and are potent antiemetics. Droperidol is a potent butyrophenone, and, similar to the others, it produces its action centrally at sites where dopamine, norepinephrine, and serotonin act.^{298,432} It has been postulated that butyrophenones may occupy GABA receptors on the postsynaptic membrane, reducing synaptic transmission and resulting in a build-up of dopamine in the synaptic cleft. In particular, droperidol results in a submaximal inhibition of the GABA_A α_1 , β_1 , and γ_2 acetylcholine receptors and full inhibition of α_2 acetylcholine receptors. This submaximal inhibition of GABA receptors by droperidol may explain the anxiety, dysphoria, and restlessness that may occur with its administration.^{298,433} An imbalance in dopamine and acetylcholine is thought to occur with subsequent alteration in normal transmission of signals in the CNS. The chemoreceptor trigger zone is the emetic center, and “red” astrocytes transport neurolept molecules from the capillary to dopaminergic synapses in the chemoreceptor trigger zone, where they occupy GABA receptors. This is thought to be the mechanism by which droperidol exerts its antiemetic effect.

PHARMACOKINETICS

Droperidol is biotransformed in the liver into two primary metabolites. Its plasma decay can be described by a two-compartment model. The pharmacokinetics^{298,434} is shown in Table 23.1.

Pharmacodynamics

EFFECTS ON THE CENTRAL NERVOUS SYSTEM

The effects of neurolept anesthetics on human CBF and CMRO₂ have not been studied. In dogs, droperidol causes potent cerebral vasoconstriction, producing a 40% reduction in CBF. No significant change in CMRO₂ occurs during droperidol administration. The EEG in conscious patients shows some reduction in frequency, with occasional slowing. Low-dose droperidol also has been shown to cause balance disturbances at the time of discharge after doses used for antiemetic prophylaxis. Droperidol may produce extrapyramidal signs and worsen symptoms of Parkinson disease, which is why the drug should be used with great caution in patients with this degenerative disorder. It also rarely may precipitate malignant neuroleptic syndrome.

EFFECTS ON THE RESPIRATORY SYSTEM

When used alone, droperidol has little effect on the respiratory system. Droperidol (0.044 mg/kg) given to surgical patients produced a slight reduction in respiratory rate, and IV droperidol (3 mg) had no significant effect on tidal volume in volunteers. More detailed respiratory studies are unavailable.

EFFECTS ON THE CARDIOVASCULAR SYSTEM

Similar to most antipsychotics, droperidol may prolong the QT interval by delaying myocardial repolarization and precipitating torsades de pointes.^{298,435} This seems to be dose dependent and may be of clinical significance when other

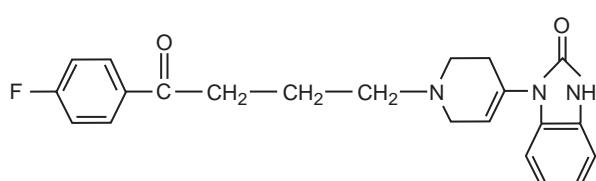


Fig. 23.23 Structure of droperidol, a butyrophenone derivative.

causes of QT prolongation also are present. Droperidol also may possess some antiarrhythmic effects that are similar to those of quinidine. Droperidol produces vasodilation with a decrease in blood pressure (see Table 23.3). This effect is considered to be a result of moderate α -adrenergic blockade. The dopamine-induced increase in renal blood flow (renal artery flowmeter methodology) is not significantly impaired by administration of droperidol. Droperidol has little effect on myocardial contractility.

USES

Use of droperidol today in the perioperative period is largely restricted to its antiemetic and sedative effects. It is an effective antiemetic; the dose for this use ranges from 10 to 20 μ g/kg IV (typically 0.6–1.25 mg for a 70-kg individual).^{298,436} Because droperidol in dosages below 1 mg produce antiemetic effects and because the cardiac side effects may be dose-dependent, an IV dose below 1 mg for prevention of PONV is advisable.⁴³⁷ These doses of droperidol, given at the start of anesthesia for operations lasting 1 hour, reduce the incidence of nausea and vomiting by about 30%. These doses given at induction have little effect on wake-up time, but should they be given at the end of surgery, there could be some residual hypnotic effect. Overall, antiemetic efficacy of droperidol alone is equal to that of ondansetron and results in an equal number of side effects, but droperidol is more cost-effective. The efficacy of droperidol as an antiemetic is enhanced when used in combination with serotonin antagonists or dexamethasone, or both. Droperidol also has been shown to be effective in the treatment and prevention of pruritus secondary to opioid administration. It has been given intravenously and into the epidural space for this purpose. When used in this fashion, droperidol also effectively reduces nausea, but it increases sedation. The safety of droperidol administration into the epidural space has not been fully evaluated, however, and it is not approved for administration via this route.

Summary

Many different IV drugs are available for use in the care of patients requiring general anesthesia or sedation. The selection of a particular drug, but more often of a combination of drugs, must be based on the individual patient's need for hypnosis, amnesia, and analgesia. Drug selection must match the physiology and/or pathophysiology of the individual patient with the pharmacology of the particular drug(s). In addition, based on the pharmacokinetic and pharmacodynamic interactions now described, optimal dosage of hypnotic-analgesic combinations may be selected. A patient in shock who requires induction of anesthesia should receive the drug that produces rapid onset of effect without causing further hemodynamic compromise. The knowledge of the clinical pharmacology of each of the IV anesthetic drugs enables the clinician to induce and maintain sedation or general anesthesia safely and effectively. There is no single perfect drug for any particular patient, but rather the informed practitioner wisely employs the appropriate drug or drugs in the practice of good anesthesia care.

Acknowledgment

The editors and publisher would like to thank Drs. J.G. Reeves, Peter S.A. Glass, David A. Lubarsky, Matthew D. McEvoy, and Richardo Martinez-Ruiz for contributing a chapter on this topic in a previous edition of this work. It has served as the foundation for the current chapter.

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24 Opioids

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KEY POINTS

- Opioids are a vital part of providing the analgesic component of anesthesia and often form the foundation for postoperative pain management.
- Opioids suppress pain by targeting multiple sites throughout the nervous system including action in brain, spinal cord, and peripheral nervous systems.
- An increased understanding of the molecular pharmacology of opioid receptors and opioid-induced cellular responses allows utilization of innovative techniques for analgesia.
- Opioids also affect multiple organ systems, including the respiratory and cardiovascular systems, and can cause a variety of adverse effects. Proper dosing and monitoring may allow these adverse effects to be minimized.
- Pharmacokinetic and pharmacodynamic properties of opioids are affected by a variety of factors, such as age, body weight, organ failure, shock, and drug interactions. To administer opioids, these factors should be taken into consideration.
- Although new opioid delivery systems such as transdermal patches provide certain clinical advantages, they can also pose additional risks such as respiratory depression.
- Opioid analgesics serve a critical role in acute pain management but their role in the long-term treatment of chronic noncancer pain has been called into question due to increased risks of overdose and addiction.

Introduction

The remarkable beneficial effects of opioids, as well as their toxic side effects and addictive potential, have been known for centuries. The term opioid refers broadly to all compounds related to opium. The word opium originates from *opos*, the Greek word for juice, the drug being derived from the juice of the opium poppy, *Papaver somniferum*. In contrast, the term opiate refers to natural products derived from the opium poppy and includes morphine, codeine, and thebaine.

The first undisputed reference to opium is found in the writings of Theophrastus in the third century B.C. During the Middle Ages, many of the uses of opium were appreciated. Opium contains more than 20 distinct alkaloids. In 1806, Sertürner reported the isolation of a pure substance in opium that he named morphine, after Morpheus, the Greek god of dreams. By the middle of the nineteenth century, the use of pure alkaloids rather than crude opium preparations began to spread throughout the medical world. Since then, there have been ongoing efforts to develop semisynthetic and synthetic opioid analgesics without the adverse side effects. Unfortunately, many of the synthetic opioids share side effects of natural opioids. The search for new opioid agonists led to the synthesis of opioid antagonists and compounds with mixed agonist/antagonist properties, which further expanded therapeutic options and provided important tools for exploring mechanisms of opioid actions. Although new methods of opioid administration, including patient-controlled analgesia (PCA) and computer-based infusion techniques, have been developed, opioids continue to act on common binding sites throughout the nervous system.

Pharmacology of Opioids

CLASSIFICATION OF OPIOID COMPOUNDS

Opioids can be classified as naturally occurring, semisynthetic, and synthetic (Box 24.1). The naturally occurring opioids can be divided into two chemical classes, phenanthrenes (morphine and codeine) and benzylisoquinolines (papaverine). The semisynthetic opioids are morphine derivatives in which one of several changes has been made. Synthetic opioids are classified into four groups, the morphinan derivatives (levorphanol), the diphenyl or methadone derivatives (methadone, *d*-propoxyphene), the benzomorphans (phenazocine, pentazocine), and the phenylpiperidine derivatives (meperidine, fentanyl, sufentanil, alfentanil, and remifentanil). Structures of opioid compounds are shown in Fig. 24.1¹ and Table 24.1¹.

Opioids can be classified as agonists, partial agonists, mixed agonist-antagonist, and antagonists on the basis of their interaction with the opioid receptors.

BASIC STUDIES ON OPIOID RECEPTORS

In 1973, three independent teams of investigators described the presence of opioid binding sites in the nervous system from the radioligand binding assays. From pharmacologic experiments, three types of opioid receptors were postulated. They were named μ for morphine type, κ for the ketocyclazocine type, and σ for the SKF10047 (N-allyl-normetazocine) type. In addition, a high-affinity receptor for enkephalins was found in the mouse vas deferens, and was named the δ -receptor. Furthermore, an ϵ -receptor was

BOX 24.1 Classification of Opioid Compounds

Naturally occurring

- Morphine
 - Codeine
 - Papaverine
 - Thebaine
- Semisynthetic**
- Heroin
 - Dihydromorphine, morphinone
 - Thebaine derivatives (e.g., etorphine, buprenorphine)
- Synthetic**
- Morphinan derivatives (e.g., levorphanol, butorphanol)
 - Diphenylpropylamine derivatives (e.g., methadone)
 - Benzomorphan derivatives (e.g., pentazocine)
 - Phenylpiperidine derivatives (e.g., meperidine, fentanyl, sufentanil, alfentanil, remifentanil)

From Bailey PL, Egan TD, Stanley TH. Intravenous opioid anesthetics. In: Miller RD, ed. *Anesthesia*. 8th ed. Philadelphia: Saunders; 2015. An imprint of Elsevier Inc., p. 865.

proposed as the binding site for β -endorphin in the rat vas deferens. Pharmacologic actions of opioids and the involved receptors have been analyzed (Table 24.2).

Since the early 1990s, molecular biologic studies have elucidated the molecular structures and signal transduction mechanisms of the opioid receptors. Four different complementary DNAs (cDNAs) have been isolated as members of the opioid receptor family.² Investigators demonstrated that three of them correspond to the pharmacologically defined μ -, δ -, and κ -opioid receptors. The fourth receptor did not bind with opioid ligands with high affinities. Later, a novel peptide, nociceptin/orphanin FQ, was identified as an endogenous agonist of the fourth member of the opioid receptor family.^{3,4} The μ -, δ -, and κ -opioid receptors and the nociceptin receptor share approximately 50% amino acid sequence homology with each other. Characteristics of three opioid receptors and the nociceptin/orphanin FQ receptor are listed in Table 24.3. Hydropathy analysis of the primary structures of the opioid receptors predicted that the opioid receptors possess seven transmembrane domains (Fig. 24.2). This is a characteristic structural⁵ feature of G-protein-coupled receptors. Crystallographic analysis revealed that the μ -, δ -, and κ -opioid receptors and the nociceptin receptor actually possess seven transmembrane domains and the agonist binds deeply within a large pocket (Fig. 24.3).⁶ Furthermore, analysis of the crystal structure of the murine opioid receptor revealed agonist-induced conformational changes in detail, providing the basis for the development of new ligands.⁷

The σ (sigma) receptor, which was previously classified as a member of the opioid receptor, was shown to be an endoplasmic reticulum-resident protein, and has been implicated in many diseases, ranging from cocaine or alcohol addiction to the most recently reported familial adult or juvenile amyotrophic lateral sclerosis. The amino acid sequence of the σ -1 receptor does not resemble that of any other mammalian proteins.⁸

Further pharmacologic classification of the μ -receptor as the μ_1 , μ_2 , and μ_3 subtypes has been proposed, but the molecular identity of these receptor subtypes still remains

to be clarified. Several possible molecular models of opioid receptor subtypes exist, including alternate splicing of a common gene product, receptor dimerization, and interaction of a common gene product with other receptor or signaling molecules.⁹ Multiple μ -opioid receptor species can be produced from a gene product of the μ -opioid receptor gene by alternate splicing (Fig. 24.4).^{10,11} Analysis of the alternate splicing products reveals differences in ligand binding and G-protein activation. However, their physiologic, pharmacologic, or clinical implications remain to be elucidated. Interestingly, it was recently reported that the analgesic action of 3-iodobenzoyl-6 β -naltrexamide, a potent analgesic against thermal, inflammatory, and neuropathic pain, is mediated by its interaction with mMOR-1G, a truncated splice variant possessing only six transmembrane segments, in mice.¹²

G-protein-coupled receptors can form dimers, homodimers (same receptor), and heterodimers (different receptor types). The existence of these homodimers and heterodimers has been shown in cultured cells and *in vivo*. Among opioid receptors (μ , δ , κ , and nociception receptors), various combinations of the molecules have been shown to form dimers, and the dimer formation has been shown to affect the ligand binding properties and signal transduction mechanisms.¹³ Physiologic and clinical implications of dimer formation of opioid receptors will be further clarified. For example, it is interesting that a bivalent ligand containing μ -agonist and δ -antagonist pharmacophores effectively bridges μ - δ opioid receptor heterodimers and exhibits enhanced efficacy and a reduced tendency for tolerance in mice.¹⁴ However, in the peripheral nervous system, μ and δ receptors are apparently expressed in different sensory neuronal subpopulations.^{15,16}

Taken together, the overwhelming evidence of opioid receptor diversity in structure, ligand binding, and distribution supports the concept they serve both essential and complex signaling roles throughout the nervous system.

GENETIC VARIATIONS WHICH INFLUENCE OPIOID EFFECTS

Several single nucleotide polymorphisms (SNPs) have been identified in the human μ -opioid receptor gene (Fig. 24.5).¹⁷ The A118G mutation, the most common of these SNPs, leads to a change in the gene product in the human μ -opioid receptors, which is an A-to-G substitution in exon 1 that results in an amino acid exchange at position 40 from asparagine to aspartate (N40D). Patients with cancer who are homozygous for the A118G variant required higher doses of oral morphine for long-term treatment of their pain.¹⁸ A118G mutation of the human μ -opioid receptor gene reduces analgesic responses to morphine-6-glucuronide (M6G), but it does not significantly affect the respiratory depression induced by M6G.¹⁹ Furthermore, morphine consumption with intravenous PCA after total abdominal hysterectomy is significantly greater in women homozygous for the A118G variant than in other patients.²⁰ In a meta-analysis involving 18 studies and more than 4600 patients, carriers of A118G were observed to exhibit higher opioid analgesic requirements.²¹ Another meta-analysis showed significant association between A118G polymorphism and susceptibility to opioid dependence or addiction in Asian populations.²²

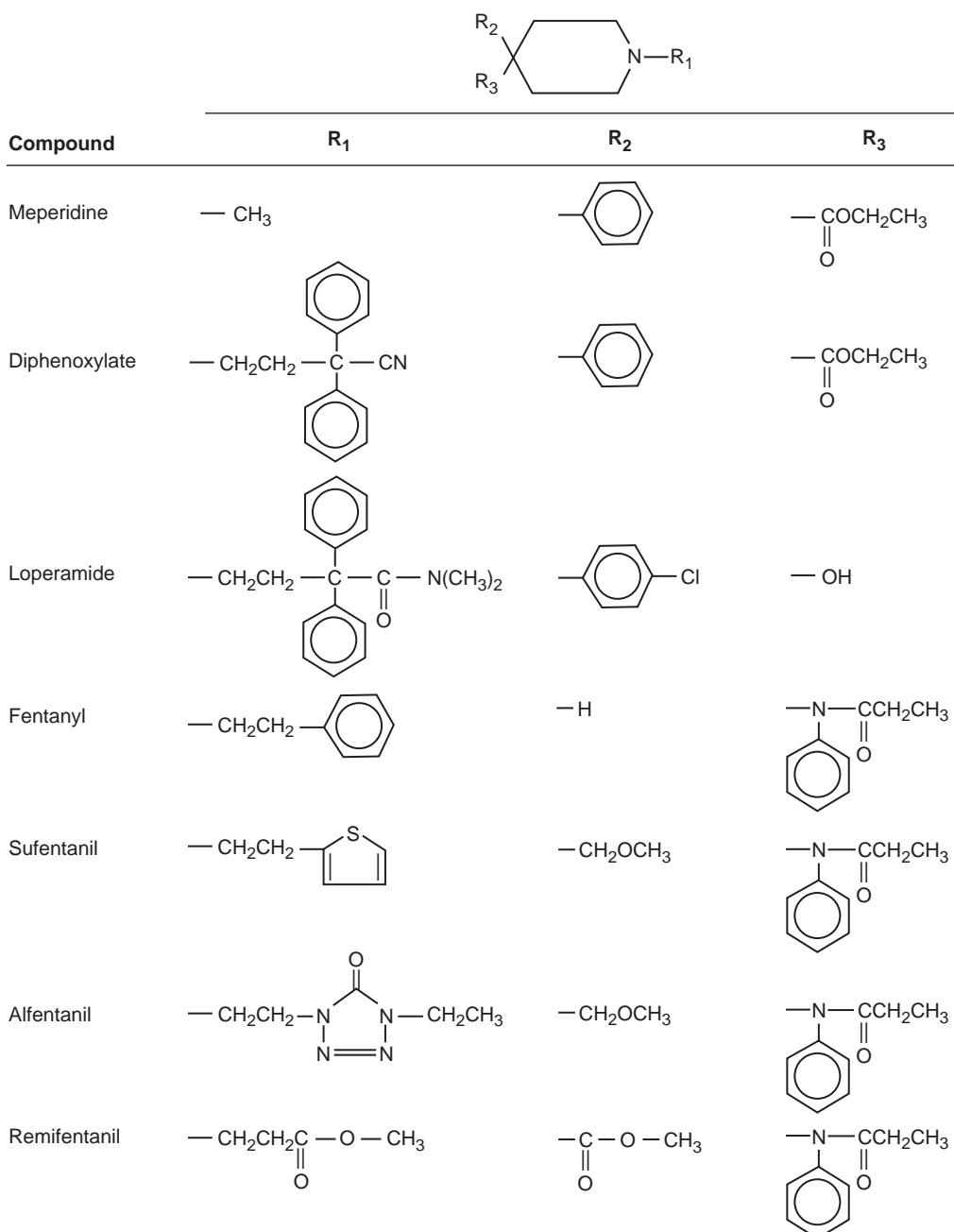


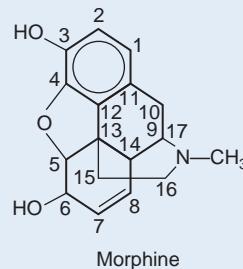
Fig. 24.1 Chemical structures of piperidine and phenylpiperidine analgesics. (From Gutstein HB, Akil H. Opioid analgesics. In: Hardman JG, Limbird LE, eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 10th ed. New York: McGraw-Hill; 2001:569–619.)

In vitro experiments show that the variant receptors with A118G mutation are associated with higher binding affinity to and potency of β -endorphin, but lower potency of morphine.²³ Studies in mouse models with analogous substitution of human A118G showed reduced analgesic response to morphine in some regions of the mouse brain with the GG genotype when compared with the AA genotype.²⁴ A study also showed that 118A messenger RNA was 1.5- to 2.5-fold more abundant than the 118G messenger RNA in heterozygous brain autopsy tissues.²⁵

Overall, these findings suggest that the 118G allele may result in changes in abundance and/or function of the μ -opioid receptor leading to differences in antinociceptive

potency of opioid analgesics. This in turn could misdirect healthcare providers in providing the most effective and safe opioid-based analgesic plan.

The C17T mutation of the human μ -opioid receptor, located in exon 1, causes an amino acid exchange from alanine to valine at receptor protein position 6 of the extracellular receptor terminal. This mutation has been reported to occur in a higher overall proportion of opioid-dependent persons, but the effects of the C17T polymorphism on analgesic responses are unknown. A recent study using cultured cells reported that adenylate inhibition via the C17T polymorphism was decreased for many opioids, including the clinically significant drugs morphine, buprenorphine,

TABLE 24.1 Structures of Opioids and Opioid Antagonists Chemically Related to Morphine

CHEMICAL RADICALS AND POSITION*

Nonproprietary Name	3	6	17	Other Changes ^t
Morphine	—OH	—OH	—CH ₃	—
Heroin	—OCOCH ₃	—OCOCH ₃	—CH ₃	—
Hydromorphone	—OH	=O	—CH ₃	(1)
Oxymorphone	—OH	=O	—CH ₃	(1), (2)
Levorphanol	—OH	—H	—CH ₃	(1), (3)
Levallophan	—OH	—H	—CH ₂ CH=CH ₂	(1), (3)
Codeine	—OCH ₃	—OH	—CH ₃	—
Hydrocodone	—OCH ₃	=O	—CH ₃	(1)
Oxycodone	—OCH ₃	=O	—CH ₃	(1), (2)
Nalmefene	—OH	=CH ₂	—CH ₂ —<	(1), (2)
Nalorphine	—OH	—OH	—CH ₂ CHKCH ₂	—
Naloxone	—OH	=O	—CH ₂ CH=CH ₂	(1), (2)
Naltrexone	—OH	=O	—CH ₂ —<	(1), (2)
Buprenorphine	—OH	—OCH ₃	—CH ₂ —<	(1), (4)
Butorphanol	—OH	—H	—CH ₂ —◆	(1), (2), (3)
Nalbuphine	—OH	JOH	—CH ₂ —◆	(1), (2)

*The numbers 3, 6, and 17 refer to positions in the morphine molecule, as shown above.

^tOther changes in the morphine molecule are as follows:

(1)Single instead of double bond between C7 and C8.

(2)OH added to C14.

(3)No oxygen between C4 and C5.

(4)Endoetheno bridge between C6 and C14; 1-hydroxy-1,2,2-trimethylpropyl substitution on C7.

From Gutstein HB, Akil H: Opioid analgesics. In: Hardman JG, Limbird LE, eds. *Goodman and Gilman's the Pharmacological Basis of Therapeutics*. 10th ed. New York: McGraw-Hill; 2001: 569–619.

and fentanyl, as well as endogenous opioids,²⁶ suggesting that this polymorphism may affect individual responses to opioid therapy, while the possible disruption of the endogenous opioid system may contribute to susceptibility to substance abuse.

It is known that genetic variation of genes other than opioid receptor genes can affect sensitivity to opioids. It has been demonstrated that the Val158Met polymorphism of the human catechol-O-methyltransferase (COMT) gene has contributed to differences in opioid consumption in patients treated for chronic cancer pain,²⁷ and is associated with variability in opioid consumption in postoperative nephrectomy patients.²⁸ COMT metabolizes biogenic amines including catecholamines such as dopamine, epinephrine, and norepinephrine, thereby acting as a key modulator of dopaminergic and adrenergic neurotransmission, and can affect the pharmacologic effects of opioids. Some studies

have explored the relationship between gene-gene interactions and opioid responses. Kolesnikov and associates have demonstrated that the heterozygous patients with μ -opioid receptor A118G and COMT G1974A mutation consumed significantly less morphine compared with homozygous patients of A118.²⁹ As investigation into the clinical impact of genetic variability continues, it is revealing that even greater complexity exists between gene-gene interactions and postoperative morphine consumption.³⁰

ENDOGENOUS OPIOID PEPTIDES

Enkephalin, β -endorphin, and dynorphin were identified as endogenous agonists for the δ -, μ -, and κ -opioid receptors, respectively. Following purification of these peptides from mammalian tissues, cDNAs for the precursors of these peptides were cloned. cDNA cloning and amino acid