Local Anesthetics

Pharmacology is one of the most tested topics on the INBDE, so a strong foundation is highly recommended. In this set of notes, we will review all of the pharmacology concepts tested on the INBDE including: amides and esters, pharmacodynamics, pharmacokinetics, calculation of local anesthetic dosage, vasoconstriction, toxicity, needle characteristics, injection techniques, classes of antibiotics, types of analgesics, and cardiovascular/ANS/CNS pharmacology.

Local anesthetics can be categorized into two main groups: **amides** and **esters**. Below, we will discuss all of the relevant information that you will need to know about local anesthetics for the INBDE.

1 Types of Local Anesthetics

Amides

- Amides are metabolized by the **liver** and their names commonly end with the suffix "**-caine**." Some important amide local anesthetics are listed below:
  - **Lidocaine (Xylocaine)**
    - Safest for use in children
    - 2% in solution
  - **Mepivacaine (Carbocaine, Polocaine)**
    - Causes the least amount of vasodilation
    - 2-3% in solution
  - **Articaine (Septocaine)**
    - Shortest duration of all the local anesthetics
    - Has an ester chain attached; it is metabolized by BOTH the liver and in plasma
    - 4% in solution
  - **Prilocaine (Citanest)**
    - Risk of methemoglobinemia (blood disorder where there is an abnormal amount of hemoglobin production) → can lead to insufficient O_2 delivery to cells
  - **Bupivacaine (Marcaine)**
    - Longest duration of all local anesthetics
    - Not safe for use in children due to prolonged soft tissue anesthesia
    - 0.5% in solution

Esters

- Esters are metabolized in **plasma** by **pseudocholinesterase** enzymes. Like amides, their names also end in the "**-caine**" suffix.
- Esters are usually more toxic and cause more allergic reactions than amides due to methylparabens.
- The following are some important esters to know for the INBDE:
  - **Benzocaine**
    - Commonly used as a topical anesthetic prior to injection
    - Risk of methemoglobinemia
  - **Cocaine**
    - Potentiates vasoconstriction
  - **Procaine**

INBDE Pro Tip:
Know the unique points associated with each local anesthetic. This is a heavily tested topic on the INBDE.

2 Pharmacodynamics/Pharmacokinetics

Pharmacodynamics

- **Pharmacodynamics** refers to the effect that a drug has on the body. Generally, local anesthetics have the following pharmacodynamic characteristics described below.
  - Sodium channel blockers:
    - Sodium channels in neurons allow the influx of sodium ions for depolarization to signal pain
    - Local anesthetics block these channels from initiating depolarization
  - Non-ionized (free-base form):
    - Only non-ionized drug forms can cross the hydrophobic neuron membrane
    - Blocking the sodium channel can only be done from inside of the cell
  - Less effective in inflamed tissue:
    - Inflamed tissue has a lower pH
    - Excess H+ ions favor an equilibrium where the drug is in an ionized form = cannot cross the neuron membrane
  - Require a critical length:
    - **Complete anesthesia** – achieved when 3 consecutive nodes of Ranvier are blocked
    - There is a better chance of anesthesia when there is a longer length of nerve bathed in anesthetic

Pharmacokinetics

- **Pharmacokinetics** describes the response that an individual's body has to a drug. Key principles of pharmacokinetics are provided below, demonstrating how the body may be impacted by local anesthetics. It is important to know these concepts for the INBDE.
  - ↑ protein binding leads to ↑ duration of action
  - ↓ pKa = faster onset of action
    - Why? ↓ pKa → drug gives up proton more easily → drug becomes non-ionized → drug crosses membrane

Drug	pKa
Mepivicaine	7.6
Articaine	7.8
Lidocaine	7.8
Prilocaine	7.8
Bupivacaine	8.1

3 Calculating Local Anesthetics

A carpule/cartridge of local anesthetic represents **1.8mL**. Therefore, local anesthesia at a concentration of **1%** has **18mg** of local anesthetic. For **100% solution** there are **1.8g** or **1,800mg** of the drug. It is important to know these numbers for the INBDE.

Example 1.31

Question: The most common local anesthetic used in dentistry is 2% lidocaine (1:100,000 epinephrine). How many mg of lidocaine are present in a carpule (1.8mL) of this iteration?

Solution:
The calculation is simple for lidocaine: 1% contains 18mg of lidocaine, hence, 18mg/1% x 2% = 36 mg of lidocaine.

Therefore, there are 36mg of lidocaine in a 2% solution.

4 Vasoconstriction & Toxicity

Vasoconstriction

- As mentioned, epinephrine and other kinds of vasoconstrictors are often packaged in solution with a local anesthetic.
- There are 3 main purposes for the addition of vasoconstrictors:
  1. Hemostasis
     - Counteracts vessel dilation of local anesthetic
  2. Longer anesthesia
     - Decreased blood flow to the injection site decreases the amount of anesthetic carried away from nerves
  3. Reduced toxicity
     - Increased blood vessel constriction decreases the systemic impact of the drug

Maximum Epinephrine Dosages

- The following are important numbers to remember for maximum dosage limits in healthy, as well as, cardiac patients:

Drug	Max dose
Healthy Patient	0.2 mg
Cardiac Patient	0.04 mg

Maximum Local Anesthesia Dosages

- The maximum dosage of lidocaine with and without epinephrine is 7mg/kg and 4.5mg/kg respectively.
- The maximum dosage of articaine with epinephrine is 7mg/kg.

Example 1.41

Question: The most common local anesthetic used in dentistry is 2% lidocaine (1:100,000 epinephrine). How many mg of epinephrine are present in a carpule of this iteration?

Solution:
With epinephrine, the amount is given as a ratio, which should first be converted into a percentage: 1/100,000 x 100% = 0.001%; hence 0.001% x 18mg/1% = 0.018mg of epinephrine.

Therefore, there are 0.018mg of epinephrine in one carpule of the iteration described above.

Needles & Injections

1 Measurements

Length

- Two options:
  - Long needle = 32mm
  - Short needle = 20mm

Diameter

- Three options:
  - 30-gauge = 0.3mm
  - 27-gauge = 0.4mm
  - 25-gauge = 0.5mm

- Larger diameter (smaller gauge) needles are often advantageous for the following reasons:
  - They do not bend or break as often
  - They provide better aspiration
    - Aspiration = lightly drawing one's finger back on the syringe to detect presence of blood (vessel perforation)

2 Injection Techniques

There are several different techniques for local anesthetic injection. Aiming to deliver the anesthetic slowly over the **course of 60 seconds** will decrease the discomfort of the patient.

Inferior Alveolar Nerve Block (IAN Block)

- Injection is in the center of the area bordered by the:
  - Coronoid notch
  - Pterygomandibular raphe
  - Upper maxillary molars
- High failure rate due to difficulty of the injection
- Numbs all of the mandibular teeth of the quadrant
- Numbs lips and gingiva of all teeth in the quadrant, except gingiva of the molar region
- Tongue is numbed in the quadrant if the lingual nerve is blocked as well

Techniques

- Vazirani-Akinosi = closed mouth technique, which can be useful in cases of truisms
- Gow-Gates = open mouth method, which blocks practically the entirety of V3

Injection Steps

1. Approach from the opposite side of the mouth towards the molars/premolars
   - Aim 10-15mm above the mandibular occlusal plane and parallel to that plane
2. Advance the needle slowly until bone is felt
3. Slowly withdraw the needle ~1mm and aspirate
4. If no blood is detected, inject at rate of 1 carpule/min

Buccal Nerve Block

- Anesthetizes soft tissue buccal to molars (the tissue the IAN block does not target)

Injection Steps

1. Inject from the buccal to the distal most molar, approximately parallel to the occlusal plane

Mental Nerve Block

- Anesthetizes soft tissue facial to anterior teeth
- Does not numb the teeth itself

Injection Steps

1. Locate the rubbery neurovascular bundle with your finger

2. Insert needle anterior to the mental foramen by the apices of the premolars
3. Aspirate and slowly inject

Incisive Nerve Block

- Anesthetizes the anterior teeth and premolars of the quadrant

Injection steps

1. Follow the same steps as the mental nerve block, inject over 20 seconds
2. Hold pressure on injection site for 2 minutes in order to increase the volume of anesthetic into the mental foramen

Posterior Superior Alveolar Block

- Anesthetizes maxillary molars and buccal tissue
- Does not numb the mesio-buccal root of the 1st molar in 28% of patients
  - ▸ Supplied by the middle superior alveolar nerve block
- High risk of hematoma due to injection being close to groups of blood vessels

Injection Steps

1. Palpate for zygomatic process and aim needle posterior to that
2. Retract cheek; and inject needle into mucosa above 2nd maxillary molar at a 45-degree angle to occlusal and vertical plane
3. Inject until the needle is 16mm in depth (half the length of a long needle)
4. Swing the needle so it is 45 degrees to the back of the maxillary tuberosity

Infraorbital Block

- Also known as **true anterior superior alveolar block**
  - ▸ Targets anterior superior and middle superior alveolar nerves
- Anesthetizes maxillary anteriors and premolars

Injection Steps

1. Inject at the mucobuccal fold directly over the 1st premolar into the infraorbital foramen

Greater Palatine Nerve Block

- Anesthetizes posterior hard palate and overlying tissue from 3rd molar to 1st premolar up to the midline
- Target needle into the greater palatine foramen
- Often painful

Injection Steps

1. Use a cotton tip to push gently along the area where the alveolar ridge meets the hard palate; the site where the cotton tip dips down is your injection site

Nasopalatine Block

- Most painful injection
- Anesthetizes the hard palate from canine to canine on the maxilla
- Most painful injection

Injection Steps

1. Inject palatal mucosa lateral to the incisive papilla

Local Infiltration

- Local anesthetic diffuses through bone to numb the terminal branching nerves entering the pulp of the tooth
- Septocaine (articaine) is often used
  - ▸ Best for bone penetration
- Works well in anterior teeth
  - ▸ Facial cortical plate is thin = better diffusion of anesthetic

Injection Steps

1. Inject the needle into the vestibule above the tooth of interest and aim for the root apex

Summary

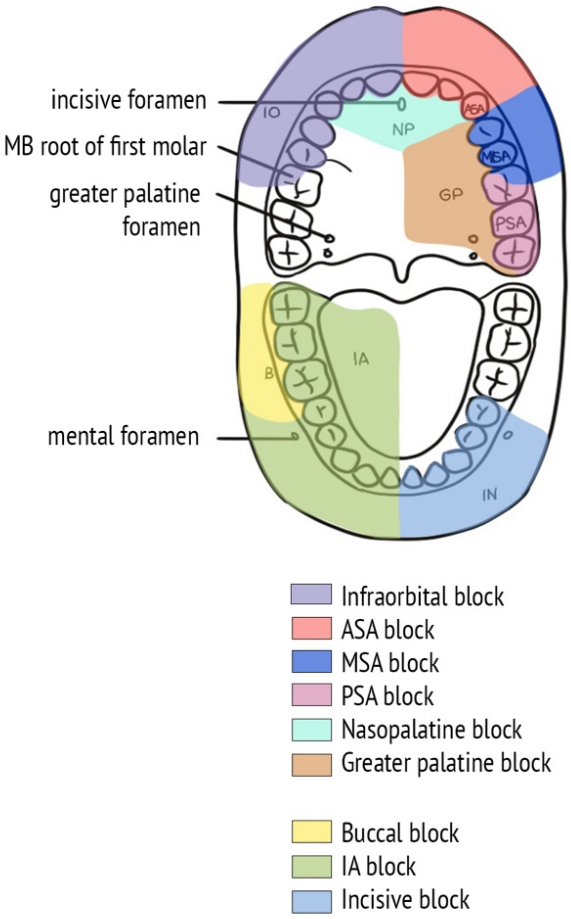

Figure 2.21 Injection sites

Antibiotics

1 Requirement of Antibiotic Prophylaxis

The use of antibiotic prophylaxis in dental practice is not common. However, there are certain instances when their use is required for invasive treatments that involve manipulation of gingival tissue or manipulation of the periapical region of a tooth.

Appropriate Use of Antibiotic Prophylaxis

- Patients with cardiac conditions:
  - Prosthetic cardiac valve
  - Previous or recurrent infective endocarditis
  - Congenital heart disease
  - Cardiac transplant patients with valvulopathy
- Consider a consultation with one's primary physician for:
  - Immunosuppression secondary to neutropenia, cancer chemotherapy, or solid organ transplant
  - Sickle cell anemia
  - High-dose corticosteroid use
  - Poorly controlled diabetes
  - Diseases of autoimmunity

2 Types of Antibiotics

Tetracyclines

- "**-cycline**" suffix
  - doxycycline, tetracycline
- Protein synthesis inhibitor – binds to 30S ribosomal subunit
- *Broadest antimicrobial spectrum
- Bacteriostatic

Carbapenems

- "**-nem**" suffix
  - Meropenem
- β-lactam – inhibits cell wall synthesis
- Bactericidal

Penicillins

- Majority have "**-cillin**" suffix
- β-lactam – inhibits cell wall synthesis
- Cross-allergenic with cephalosporins
  - Penicillin is chemically related, so the immune system might see them both as the same if the patient is allergic to either one
- Bactericidal

The following are specific types of penicillin and their associated characteristics:

1. **Penicillin V** – oral administration
2. **Penicillin G** – IV administration
3. **Amoxicillin** – broad spectrum
4. **Augmentin** – includes amoxicillin and clavulanic acid (works against β-lactamase resistant bacteria)
5. **Carbenicillin** – for use against pseudomonas

Monobactams

- "**-am**" suffix
  - Aztreonam
- β-lactam – inhibits cell wall synthesis
- Bactericidal

Cephalosporins

- "**Ceph-**" prefix
- β-lactam – inhibits cell wall synthesis
- Grouped into generations based on their spectrum against specific bacteria
  - 1st Gen = Cephalexin (Keflex)
  - 2nd Gen = Cefonicid
  - 3rd Gen = Ceftriaxone
  - 4th Gen = Cefepime
- Bactericidal

Fluoroquinolones

- "**-floxacin**" suffix is common
  - Ciprofloxacin
- DNA synthesis inhibitor
- Bactericidal

Sulfonamides

- "**Sulfa-**" prefix
  - Sulfisoxazole
- Folate synthesis inhibition
  - Results in folate deficiency that impacts DNA synthesis
- Bacteriostatic

Macrolides

- "**-thromycin**" suffix
  - Azithromycin
- Protein synthesis inhibitor – binds to 50S ribosomal subunit
- Bacteriostatic

Lincosamides

- "**-mycin**" suffix
  - Clindamycin, Lincomycin
- Protein synthesis inhibitor – binds to 50S ribosomal subunit
- Bacteriostatic

3 Medical Prescriptions (Rx)

Prescription of antibiotics will vary with each patient based on their age, medical history, current medications, and other factors.

Rx for Infective Endocarditis Prophylaxis

Patient / Case	Rx	Time of Admin
First choice	Amoxicillin 2g	60 mins prior to tx
Children	Amoxicillin 50mg/kg	60 mins prior to tx
Penicillin allergy	Azithromycin 500mg	60 mins prior to tx
Children with Penicillin allergy	Azithromycin 15mg/kg	60 mins prior to tx
IV	Ampicillin 2g	30 min before tx
Children, IV	Ampicillin 50mg/kg	30 min before tx

Rx for Prosthetic Joint Prophylaxis

Antibiotic prophylaxis before dental treatment is no longer recommended for prevention of prosthetic joint infections according to the ADA.

Side Effects

Knowing the side effects of antibiotics is not only important for general knowledge, but is also important when considering prescriptions.

- For example, it is best not to prescribe tetracycline to a patient with liver disorders

Side Effect	Associated Antibiotic
Pseudomonas colitis	Clindamycin
Superinfection	Very broad-spectrum antibiotics
Aplastic anemia	Chloramphenicol
Liver damage	Tetracycline

Drug Interactions

The following drug combinations are not recommended and should not be prescribed:

1. Bactericidal and bacteriostatic drugs
   - Bactericidal kills bacteria when they are rapidly growing; bacteriostatic drugs inhibit this rapid growth = the drugs cancel each other out
2. Antibiotics and oral contraceptives
   - Antibiotics suppress normal gastrointestinal flora involved in recycling of active steroids in the contraceptive
3. Penicillin and probenecid
   - Probenecid alters renal clearance of penicillin
4. Tetracycline + antacids/dairy
   - Antacids and dairy reduce the absorption of tetracycline via calcium/ion binding
5. Broad-spectrum antibiotics and anticoagulants
   - Anticoagulants' actions are enhanced

Drug Concentration

- Tetracycline concentrates well in gingival crevicular fluid
- Clindamycin concentrates well in bone

Antivirals & Antifungals

The following are common antivirals and antifungals prescribed in dental practice:

- Acyclovir, Valcyclovir
  - "**-vir**" = antiviral
  - Used for herpes
- Fluconazole
  - "**-azole**" = antifungal
  - Used for Candidiasis

Analgesics

1 Acetaminophen

Acetaminophen is commercially known as Tylenol, and there are several key points to know about this drug.

- Maximum daily dose = 4,000 mg
- Inhibits pain in the central nervous system
- Drug of choice for a feverish child
  - Aspirin is known to cause Reye's Syndrome
- Negatively impacts the liver
  - Toxic at higher doses
  - Greater damage when combined with alcohol

2 NSAIDS

Types of NSAIDS

NSAIDS work by inhibiting COX 1 and/or COX 2. Normally, COX1 and COX2 promote inflammation by generating prostaglandins (PG). By blocking COX1 and 2 there is a corresponding reduction in the effects of PGs. Below is a table summarizing important NSAIDS to study for the INBDE.

Name	Blocking	Association
Aspirin (ASA)	COX 1 & 2 (irreversible)	Impacts GI
Ibuprofen (Motrin, Advil)	COX 1 & 2 (reversible)	Impacts kidney
Naproxen (Aleve)	COX 1 & 2 (reversible)	
Ketorolac (Acular)	COX 1 & 2 (reversible)	IV, IM, or oral route
Celecoxib (Celebrex)	COX 2	
Meloxicam (Mobic)	COX 2	Treatment of arthritis

Therapeutic Effects of Aspirin

- Anti-inflammatory and analgesic
  - Inhibits COX 1 & 2 (PG synthesis)
- Antipyretic
  - Inhibits PG synthesis in the hypothalamus (temperature regulation center)
- Inhibits clotting
  - Inhibits TXA2 synthesis = inhibits platelet aggregation

The mechanism of action for aspirin is very important to know and highly testable on the INBDE.

Toxic Effects of Aspirin

- GI bleeding
- Metabolic acidosis
- Salicylism
- Tinnitus
- Nausea & vomiting
- Delirium
- Hyperventilation

INBDE Pro Tip:
The maximum daily dose of ibuprofen is 3,200 mg.

3 Steroids

Corticosteroids

Corticosteroids are man-made steroids, which mimic the action of cortisol (produced in the adrenal cortex of the adrenal gland); the common suffix of corticosteroids is "**-sone.**"

- Prednisone
- Dexamethasone
- Hydrocortisone

Therapeutic Effects

- Analgesic and anti-inflammatory
  - Inhibits phospholipase A2 = inhibits arachidonic acid synthesis

Side Effects of Steroids

- Immunosuppression if used chronically
- Gastric ulcers
- Osteoporosis
- Fat redistribution
- Hyperglycemia
- Acute adrenal insufficiency
  - Follows the **Rule of Twos**
    - Adrenal suppression can occur if a patient is taking 20mg of cortisone (or its equivalent) for 2 weeks within 2 years of dental treatment
    - Patient may need supplemental doses of steroids prior to therapy

4 Narcotics/Opioids

Types of Narcotics

- Codeine
- Hydrocodone
- Oxycodone
- Oxycontin
- Meperidine
- Morphine
- Tramadol
- Fentanyl
- Sufentanil
- Heroin

Combination Narcotics Therapeutic Effects & Side Effects of Morphine

The effects of morphine can easily be memorized using the following acronym:
Miosis (pupil constriction)
Out of it (sedation)
Respiratory depression
Pneumonia (aspiration pneumonia)
Hypotension
Infrequency of urination & constipation
Nausea & vomiting
Euphoria & dysphoria

Overdose & Addiction

The following drugs can be used when an overdose or addiction of morphine occurs:

- Naloxone
  - Competitive opioid antagonist, for emergencies
- Naltrexone
  - Antagonist, treats addiction

In emergencies, the half-life of naloxone may be shorter than the half-life of the opioid, therefore, multiple doses of naloxone may be required.

INBDE Pro Tip:
Methadone is a synthetic opioid agonist that can be used not only for relief of pain, but also, for opioid addiction.

Drug Schedule

Drugs and substances are classified into five schedules or categories based on their potential to be abused. Substances in the Schedule I category have the highest abuse potential. Examples of opioids in various categories are included in the table below, but note that these schedules are not exclusive to opioids.

Name	Opioid
Schedule I	Heroin
Schedule II	Oxycodone, fentanyl, meperidine
Schedule III	Acetaminophen + codeine
Schedule IV	Tramadol
Schedule V	Cough medicines with codeine

5 Nitrous Oxide

Nitrous oxide is commonly known as laughing gas, and is often stored in a blue-colored tank in dental offices. The following are a few characteristics of nitrous oxide:

- Tingling sensation before onset
- A flow rate of 5-6L is generally acceptable
- Patient must breathe through their nose
- Nausea (side effect)
- Peripheral neuropathy from longterm exposure
- Minimum alveolar concentration (MAC) = 105%
  - **MAC** – concentration in alveoli required for 50% of patients to be immobile
  - Impossible to go over 100%, so 105% implies that N_2O has very low potency
- Diffusion hypoxia
  - N_2O can get trapped in lungs
  - Always give patient 100% O_2 for 5 minutes to eliminate N_2O from the body

Pharmacokinetics

1 Steps of Pharmacokinetics

Pharmacokinetics, in simple words, is the study of what the body does to a drug. Pharmacokinetics does not study what the drug binds to nor its therapeutic or toxic effects. After administration, the following are the sequential steps of a drug's path through the body:

1. Absorption
2. Distribution
3. Metabolism
4. Elimination

Routes of Administration

- Enteral: oral, sublingual, or rectal
- Parenteral: intravenous, intramuscular, or subcutaneous
- Other routes: intranasal, inhalation, topical, or vaginal

Absorption

Generally, drugs must cross several epithelial or endothelial cell layers (barriers) to enter the body in order for absorption to take place. Different methods of administration determine which barriers the drug must cross to enter to be absorbed. Below are a few facts to know:

- Epithelial cell layers must be crossed when administering drugs to be absorbed through the skin, intestines, respiratory system, and genitourinary tract
- Endothelial cells must to be crossed for drugs to reach blood vessels
- Local drugs are active at the site of administration/absorption
- Systemic drugs must enter the bloodstream to reach the rest of the body
  - ▸ Cross cell lumen → apical membrane → basolateral membrane → interstitium → endothelial lining → reaches bloodstream
- 100% bioavailability can only occur if a drug is administered intravenously (IV)

pH is also important to consider when discussing drug absorption. The ways in which an acidic or basic drug interacts with its environmental pH can alter the charge of the drug and subsequently its absorption.

Generally, drugs should be of neutral charge for absorption to take place.

- Weak acids: pH < pKa for absorption
- Weak bases: pH > pKa for absorption

	Acidic Drug	Basic Drug
Acidic Environment	Non-ionized	Ionized
Basic Environment	Ionized	Non-ionized

- We want the drug to be non-ionized for it to be absorbed at the appropriate location

Distribution

- For adequate systemic distribution, a drug must first reach the blood stream
  - ▸ Topical drugs are an exception to this rule
- Once the drug arrives at the target tissue, it passes through endothelial cells, cellular interstitium, and finally the basolateral membrane of the tissue cell type
- Systemic drugs normally reach vessel-rich organs quickly for example:
  - ▸ Heart, liver, and lungs

First Pass Effect

- Drugs absorb through the GI system and are sent from the hepatic portal system to the liver
- The liver metabolizes the drug, leaving a smaller fraction of the drug to travel through the circulatory system
- Oral drugs undergo the above noted process, which is known as the "First Pass Effect"

Volume of Distribution (V_d)

- Volume (L) of total body water in which a drug will partition
- Describes the distribution of a drug across three body water compartments
  - Plasma (4%)
  - Interstitial (16%)
  - Intracellular (40%)
- People who have less body water than the average male adult should be given a lower drug dose to properly aid distribution
  - Women
  - Obese
  - Elderly
- Brain and muscle have the highest water content, while adipose tissue has the lowest water content

Metabolism

Metabolism refers to the way a drug is chemically altered and inactivated in the body. There are two main phases of drug metabolism reactions:

Phase I

- Functionalization (oxidation, reduction, hydrolysis)
  - Oxidation is the most common
- Achieved through Cytochrome P450 (CYP450) enzymes

Phase II

- Conjugation (glucuronide, glutathione, glycine)
  - Covalently adds polar side chains to the drug
  - Glucuronide is the most common side chain added via **UDP-glucuronosyltransferase**

Phase I and II reactions share the following common characteristics:

- Drugs sometimes go through both phases or just one phase
- Both phases decrease the efficacy of the drug/inactivate the drug
- Both phases increase drug polarity, which prevents passive diffusion and facilitates renal and GI clearance of the drug

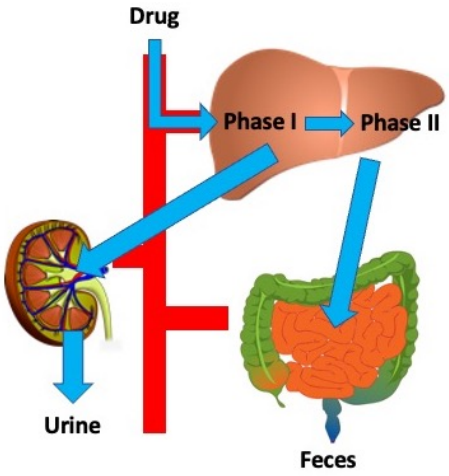

Figure 5.11 Drug metabolism

Elimination

Elimination refers to how a drug is removed from the body

- Elimination occurs mostly in the kidneys
- Phase I creates polar molecules, which go to the kidneys for urinary clearance
- Phase II creates polar and larger molecules, which tend to clear in the GI tract as feces

2 Drug-Drug Interactions

When drugs interact, one drug can affect the pharmacokinetics of the other drug. These interactions normally occur in the metabolism phase. There are commonly two kinds of effects from drug interactions:

- **Induction:** drug A induces liver cytochrome enzymes = ↑ metabolism = ↓ effect of drug B
- **Inhibition:** drug A competes for metabolism or inhibits liver cytochrome enzymes = ↓ metabolism of drug B = ↑ toxicity of drug B

Dental Drug	Interacting Drug	Interaction risk
NSAIDS	Lithium	↑ lithium toxicity
NSAIDS	Hypotensives	↓ effect of hypotensive
NSAIDS	Anticoagulants	↑ risk of bleeding
Penicillins	Oral contraceptives	↓ oral contraceptive effect
NSAIDS	Methotrexate	↑ methotrexate toxicity
Metronidazole	Warfarin	↑ risk of bleeding

Examples of Dental Drug-Drug Interactions

Factors Influencing Drug Effectiveness

The effect of the same drug can vary amongst different people due to several factors:

1. Prescribed dose
   - Medical errors
   - Patient compliance
2. Administered dose (effected by pharmacokinetics)
   - Absorption
   - Distribution
   - Metabolism
   - Elimination
3. Active dose (effected by pharmacodynamics)
   - Drug-receptor interaction
4. Intensity of effect

Pharmacodynamics

Pharmacodynamics, in simple words, is the study of the effects that drugs have on the body. These effects can be viewed from two different perspectives:

1. **Drug targets –** these are often protein carriers, channels, enzymes, or receptors
2. **Drug interactions –** these often involve agonists, inverse agonists, and antagonists

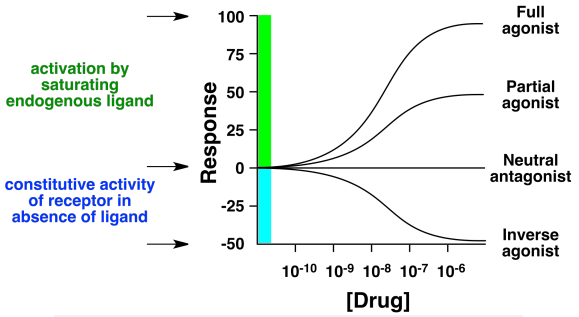

Figure 6.11 Response Curve

1 Interactions

Agonists

Agonists mimic the effects and cause the same actions as an endogenous agonist molecule. Agonists can produce a full 100% of its intended effect **(full agonist)** or less than 100% **(partial agonist).**

Antagonist

Antagonists work opposite to agonists in that these will inhibit the action of the endogenous agonist. The mechanism in which this inhibition occurs is through 2 main ways:

1. **Competitive antagonist –** competing directly with an agonist for the **same** binding site located on the receptor. This site is called an active site.
2. **Non-competitive antagonist –** binds to a position other than the active site, while preventing the agonist from binding. Oftentimes, non-competitive antagonism will change the shape or conformation of the receptor at the active site.

Inverse Agonist

Inverse agonists do not bind at the same active site as an agonist (preventing their interactions) but will produce an effect that is opposite that of the agonist

2 Dose-Response Curves

Type I Dose-Response Curve

A **type I dose-response curve** is used to correlate the response/efficacy of a drug (y-axis) to the drug dose (x-axis). Its shape can either be log form or hyperbolic.

A dose-response curve can be used to describe drug characteristics as follows:

- **Intrinsic activity (E_{max}) –** maximal effect of a drug
  - Full agonist E_{max} = 1
  - Partial agonist E_{max} = 0-1
  - Antagonist E_{max} = 0
- **Efficacy** – effect of a drug when it binds to the target
- **Affinity** – level of attraction of a drug to its receptor
  - **Dissociation constant (K_d)** – concentration of drug needed to occupy 50% of receptors
  - Lower K_d represents a higher or greater affinity
- **Potency** – strength of a drug at a certain concentration
  - **Effective concentration (EC50) –** describes the concentration at which half the maximal effect is achieved
  - The more potent the drug, the lower the EC50

The presence of antagonists may change the shape of the type I dose-response curve

- Competitive antagonists will shift the curve to the RIGHT
- Non-competitive antagonists will shift the curve DOWN

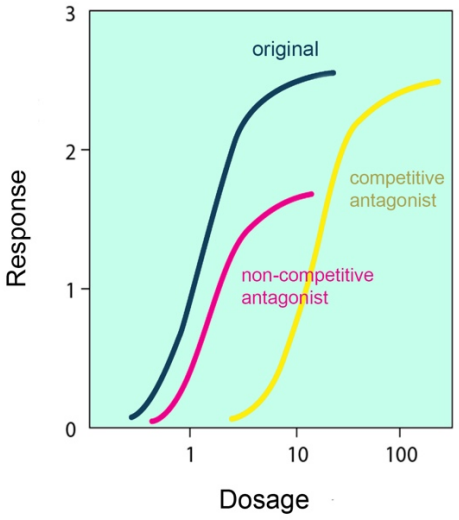

Figure 6.21 Type 1 Response

Type II Dose-Response Curve

In a **type II dose-response curve**, the x-axis measures the drug dose; and the y-axis measures the quantity of subjects responding to the drug.

Type II dose-response curves can show 3 different curves representing the following scenarios:

- **Therapeutic effect curve**
  - **ED50** – dose at which the desired effect effect is produced in 50% of the population
- **Toxic effect curve**
  - **TD50** – dose at which a toxic effect is produced in 50% of the population
- **Lethal effect curve**
  - **LD50** – dose at which a lethal effect is produced in 50% of the population

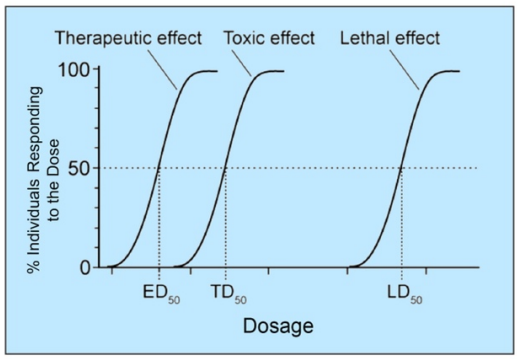

Figure 6.22 Type 2 Response

Therapeutic Index (TI) is an indicator of drug safety. A larger index indicates a safer drug, as it implies a larger difference in dose between the therapeutic dose and the toxic dose.

- In animal studies…. **TI = LD50/ED50**
- In human studies…. **TI = TD50/ED50**

3 Effects of Drug Interaction

Additive

- Drugs interact to combine their individual degrees of effect
- Effects are combined

Antagonist

- Drugs interact to lessen the effect than if one drug were to be used alone
- **Chemical antagonism** – a drug binds to another drug to prevent the other's function
- **Receptor antagonism** – competition between two drugs for the same receptor
- **Pharmacokinetic antagonism** – one drug affects the pharmacokinetics of another drug
- **Physiologic antagonism** – two drugs with opposing effects on the same tissue on distinct receptors

Synergist

- Combining drugs leads to a greater effect than the sum of their independent effects

Autonomic Nervous System

1 ANS Physiology

The sympathetic nervous system (SNS) and parasympathetic nervous system (PNS) are branches of the ANS. In many systems they have opposing effects.

- SNS effects promote "fight or flight"
- PNS effects promote "rest and digest"
- Some important exceptions to this rule are:
  - The vasculature to skeletal muscles are controlled by the SNS
  - The sweat glands are controlled by the SNS

All nerve pathways originate from the CNS (brain & spinal cord)

- 12 cranial nerves – PNS
- 0 cervical nerves – autonomic nerves do not originate here
- 12 thoracic nerves – SNS
- 5 lumbar nerves – SNS
- 5 sacral nerves – PNS

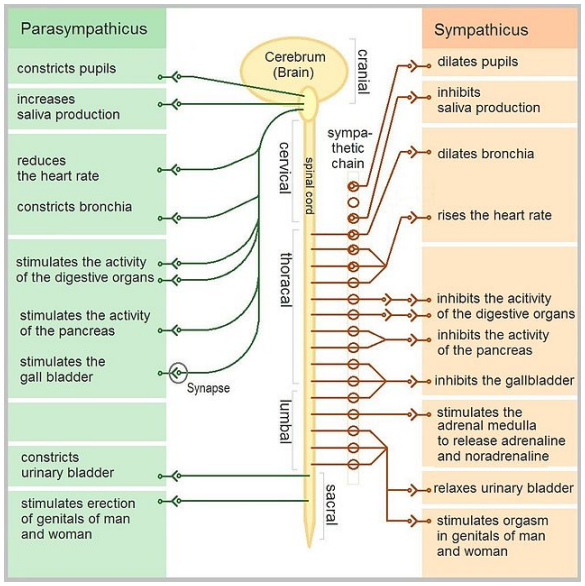

Figure 7.11 Autonomic Nervous

The following are examples of the opposing effects of the SNS and PNS:

Fight or Flight (SNS)	Rest & Digest (PNS)
Slows digestion	Increases digestion
↑ Heart rate	↓ Heart rate
↓ Saliva production	↑ Saliva production
Pupillary dilation	Pupillary constriction
Bladder relaxation, decrease urination	Bladder constriction, increase urination
Bronchi dilation	Bronchi constriction

2 Receptors in the ANS

Receptors in the ANS can be described in different ways.
Ionotropic – ion channel
Metabotropic – G-protein coupled receptor (GPCR)

- 7-transmembrane domain
- Activates a secondary messenger system
- All receptors in target organs of the autonomic nervous system are metabotropic

Receptors in the ANS are most often referred to as cholinergic and adrenergic.

- **Cholinergic –** responds to acetylcholine (Ach) and are found in the PNS and SNS
  - **Nicotinic (nAchR)**
    - Also binds nicotine, ionotropic
    - All receptors in the medulla + ganglion
  - **Muscarinic (mAChR) –**
    - Also binds muscarine, GPCR
- **Adrenergic** = binds epinephrine and norepinephrine, GPCR
  - Receptors in the SNS

SNS vs. PNS

Differences between the SNS and PNS can be distinguished by the following methods:

- Effect on organs
  - **SNS –** fight or flight
  - **PNS –** rest and digest
- The spinal cord region they originate in
  - **SNS –** thoracolumbar
  - **PNS –** craniosacral
- Neurotransmitters used
  - **SNS –** Ach to ganglion, NE from nerves and Epi/NE from adrenal gland
  - **PNS –** Ach throughout
- Neurotransmitter receptors used
  - **SNS –** adrenergic metabotropic receptors at target organs
  - **PNS –** muscarine metabotropic receptors at target organ
- Length of pre & postganglionic neurons
  - **SNS –** short preganglionic to sympathetic trunk, long post-ganglionic
  - **PNS –** long preganglionic, short postganglionic

Synthesis of Neurotransmitters

- **Acetyl CoA + choline = acetylcholine**
  - The enzymes involved in the creation and breakdown of acetylcholine are acetyltransferase and acetylcholinesterase respectively

- **Tyrosine → L-DOPA → dopamine → NE → Epi**
  - Catecholamines = dopamine, NE, epi
  - Monoamines = dopamine, NE, epi, serotonin (5-HT), histamine

Muscarinic Receptors

There are different types or **isoforms** of muscarinic post-ganglionic receptors, differentiated by their target organ.

1. M1 = CNS – autonomic ganglia
2. M2 = heart
   - Bradycardia = ↓ heart rate + electrical conduction
3. M3 = smooth muscle & exocrine glands
   - Salivation, urination, defecation, sweating
   - Smooth muscle contraction
   - Vascular endothelium vasodilation
4. M4 = CNS
5. M5 = CNS

3 M Agonist Drugs

M agonists activate muscarinic receptors in the PNS. Some are non-selective to target all M receptors, while others are selective to certain M receptor types.

- Non-selective M agonists will effect M1-5 receptors if systemic in its distribution, and should not be used systemically in patients with these following conditions:
  - **Asthma/COPD –** these conditions result in airflow obstruction to the lungs. Muscarinic agonists can cause bronchoconstriction, thereby exacerbating the disease
  - **Peptic ulcers –** muscarinic agonists can cause an increase in the secretion of gastric acid, worsening peptic ulcers
  - **Coronary Heart Disease –** the cardiac inhibition observed with muscarinic agonists can worsen cases of coronary heart disease
  - **Hyperthyroidism –** muscarinic agonists can depress the cardiac system, causing the body to compensate and release epinephrine. Epinephrine in patients with hyperthyroidism can cause arrhythmias.

M-Agonists List

Direct acting	Activates M-receptor
Pilocarpine	Used to stimulate saliva or eye drops to constrict pupils and reduce pressure

Indirect acting	Non-competitively inhibits acetylcholinesterase
Physostigmine & Neostigmine	Reversible inhibit cholinesterase
Insecticides and Nerve gases	Irreversibly inhibits cholinesterase. High poison potential! Treatment with Pralidoxime

M-Antagonists/Ganglionic Blockers

Competitive Inhibitors	Block Muscarinic receptor, compete with acetylcholine
Scopolamine	Helpful in the reduction of saliva
Atropine	Helpful in the reduction of saliva, as well as the treatment of acute bradycardia.

4 Nicotinic Antagonist Drugs

Non-depolarizing	Allosteric inhibitor
Mecamylamine & Hexamethonium	Previously used as an antihypertensive

N-Antagonists/Neuromuscular Blockers

Neuromuscular blockers block nicotinic receptors of the somatic nervous system.

Depolarizing	Irreversible N-antagonist
Succinylcholine	Relieve laryngospasm & helps to facilitate tracheal intubation during surgery

5 Sympathetic Nervous System

In the sympathetic nervous system, epinephrine (epi) and norepinephrine (NE) act on the effector organs to elicit the fight or flight autonomic response. These neurotransmitters are synthesized through the following process:

Tyrosine → L-DOPA → dopamine → NE → Epi

- Dopamine, Epinephrine, Norepinephrine = catecholamines
- Dopamine, Epinephrine, Norepinephrine, serotonin (5-HT), histamine = monoamines

Adrenergic Receptors

There are different types of adrenergic post-ganglionic receptors based on the organ they effect:

1. α1 – smooth muscle in blood vessels
   - Vasoconstriction, urinary retention, pupil dilation (mydriasis)
2. α2 – smooth muscle in blood vessels
   i. Vasoconstriction

3. ß1 – heart
   - ↑ cardiac output, heart rate, electrical conduction, and strength of contraction
   - Renin release from kidneys, leading to vasoconstriction
4. ß2 – smooth muscle
   - Bronchodilation, vasodilation, thickened salivary secretions

Adrenergic Agonist

Name	Receptor Activated
Phenylephrine (Sudafed)	α1, reduces swelling through peripheral vasoconstriction
Norepinephrine	α & ß1 receptors
Epinephrine	α & ß receptors
Albuterol	ß2 receptor, bronchodilator used as an emergency inhaler for asthma

Adrenergic Antagonist

Name	Receptor Blocked
Phentolamine	Blocks all α receptors, used in the reversal of soft tissue anesthesia
Chlorpromazine (CPZ)	α1 receptor
Metoprolol & Atenolol	ß1 receptor (cardioselective)
Propranolol	ß receptors, prolongs lidocaine duration

Sympathomimetics

Sympathomimetics are agents that are used in order to increase the effects of endogenous catecholamines. They can be direct (act at an adrenergic receptor) or indirect (by other means).

Name	Effect
Amphetamine & Ephedrine	Stimulates release of stored norepinephrine
Tricyclic antidepressants	Inhibits reuptake of serotonin & norepinephrine
Monoamine oxidase inhibitors	Prevents the breakdown of monoamines
Methylphenidate	Psychostimulant for AHD, prevents the reuptake of monoamines
Cocaine	Prevents the reuptake of monoamines

Sympatholytics

Sympatholytics oppose the effects of neuron firing at effector organs by the sympathetic nervous system. This can be done through any mechanism. With this definition, one could argue that adrenergic antagonists are also considered sympatholytics.

Name	Effect
Guanethidine	Inhibits release of catecholamines
Reserpine	Depletes the stored not epinephrine
Clonidine & Metyldopa	α2 agonist (CNS) which blocks SNS signal. It is NOT potentiating the SNS signal

Epinephrine Reversal

- Epinephrine has a vasoconstrictive effect
- In the presence of an alpha blocker, such as phentolamine, β2 vasodilatory effect dominates and becomes the major vascular response

Cardiovascular Pharmacology

1 The Circulatory System

The human circulatory system is a system which consists of a heart (the pump) pumping blood (the fluid) through vessels (the tubing) to their target organs.
Another way to describe the circulatory system is as follows

- Heart = **cardiac output (CO)**
- Vessels = **peripheral resistance (PR)**
- Blood = **blood volume (SV)**

Blood pressure (BP) and cardiac output (CO) can be calculated using the following formulas:

BP = CO X PR
CO = SV X HR

Additional terms include:

- **Preload** – the amount of filling pressure of the heart at the end of diastole
- **Afterload** – the pressure the heart gives to eject the blood during systole
- **Systole** – period of heart contraction and ejection
- **Diastole** – period of heart relaxation and filling

2 Cardiovascular Drugs

Antihypertensives

Antihypertensives are used in treatment of high blood pressure and have several different mechanisms of action.

1. **Diuretics** block renal absorption of sodium increases urination and fluid loss = ↓ BP
   - **Furosemide** – acts on the ascending limb of the Loop of Henle
   - **Hydrochlorothiazide** (HCTZ) – thiazide (hypokalemia) acts in distal tubule
   - **Spironolactone** – K+ sparing (hyperkalemia) acts in collecting duct
2. **Hydralazine** causes vasodilation by opening K+ channels in cells and allowing easier flow of blood
3. **Calcium channel blockers** block influx of calcium in cells to cause vasodilation
   - **Verapamil**
   - **Amlodipine**
   - **Nifedipine**
4. **ACE inhibitors** inhibits the conversion of angiotensin I → angiotensin II (potent vasoconstrictor)
   - **"-prils"** (suffix)
5. **Angiotensin receptors blockers (ARBs)** competitive antagonist at angiotensin II receptor
   - **"-sartans"** (suffix)

Antihypertensive drugs	Side Effects
Diuretics	Xerostomia, nauseas
Adrenergic Blocking Agents	Xerostomia, depression, sedation, sialadeuosis
	Lichenoid reaction
Angiotensin-Converting Enzyme Inhibitors (ACEIs)	Lichenoid reaction, burning mouth, loss of taste
Calcium Antagonists	Gingival hyperplasia, xerostomia
Other Vasoldilators	Cephalgia, nauseas

INBDE Pro Tip:
It's easier to understand the mechanism of action of ARBs and ACE inhibitors by learning the process of angiotensin II synthesis.

Angina Management

Anti-angina medications help to treat individuals who have insufficient oxygen to supply the heart.

1. **Propranolol** – reduces oxygen demand by reducing heart stimulation, resulting in reduced heart rate
2. **Nitroglycerin** – vasodilation of the coronary arteries to aid in increasing oxygen supply. The use of phosphodiesterase-5 (PDE5) inhibitors (ex: Sildenafil (Viagra®)) is contraindicated in patients
3. **Calcium Channel Blockers** – reduces oxygen demand by reducing peripheral resistance via vasodilation and decreasing the contraction force of the heart

Anti-Cardiac Heart Failure Drugs

Anti-cardiac heart failure drugs are used to help pump blood through the heart during heart failure.

1. **Cardiac glycosides** work by blocking Na+/K+ ATPase to increase calcium influx and promote positive force in cardiac muscle cells. An example of a cardiac glycoside is:
   - **Digoxin**

Anti-arrhythmic

An arrhythmia is simply an irregular heart beat. With this being said, anti-arrhythmic drugs work to suppress and treat the irregular or abnormal rhythms of the heart.

There are 4 classes of anti-arrhythmic drugs:

- **Class I** - Na+ channel blockers for cardiac muscle only
- **Class II** – Beta-blockers
- **Class III** – Potassium-channel blockers
- **Class IV** – Calcium channel blockers (CCBs)

Central Nervous System

1 Central Nervous System

CNS drugs target receptors in the brain and spinal cord. In the CNS, there is a continuum of excitability from too little stimulation to excessive stimulation. Generally, from low to high excitability, the continuum is:

Anesthesia → sedation → **homeostasis** → activation → excitation → seizure

2 CNS Drugs

Antipsychotics

Antipsychotics, known as neuroleptics in some circles, are used when the brain is too active. This can include conditions such was schizophrenia, and psychosis. They work through two main mechanisms of action:

1. **Dopamine D2 receptor blockers –** blocking the dopamine receptors of the brain to decrease the effect of dopamine. Haloperidol and chlorpromazine are two examples in this category with a main side effect being tardive dyskinesia.
2. **Serotonin 5-HT receptor blockers –** inhibition of serotonin receptors all along the central nervous system. These tend to bind long enough to produce their anti-psychotic effects, but not too long so that their side effects are kept low.

INBDE Pro Tip:
Xerostomia is the most likely oral side effect of antipsychotic medications.

Antidepressants

Antidepressants are used to increase stimulation, an opposite of antipsychotics

- This is achieved through increasing the number of **monoamines** (dopamine, epinephrine, norepinephrine, serotonin, histamine) in the brain
- Generally, all antidepressants have anticholinergic side effects, because an excess can activate adrenergic receptors in the ANS

Some examples of classes of antidepressants and medications that fall into them include:

- **SSRI –** selective serotonin reuptake inhibitor
  - **Fluoxetine**
- **SNRI –** serotonin and NE reuptake inhibitor
  - **Duloxetine**
- **TCA –** tricyclic antidepressants
  - **Amitriptyline**
- **MAOI** – monoamine oxidase inhibitors
  - **Phenelzine**
- **NDRI** – norepinephrine-dopamine reuptake inhibitor
  - **Bupropion**

General Anesthetics

General anesthetics induce a coma in patients during surgery. The onset of anesthesia is inversely proportional to the solubility of the anesthetic in blood. There are 4 stages of general anesthesia:

1. Stage I – analgesia/feeling better
2. Stage II - delirium
3. Stage III – surgical anesthesia
4. Stage IV – medullary paralysis

GA example: **Halothane** can be toxic to the liver

Anxiolytics/Sedatives

1. Benzodiazepines

- ↑ GABA binding and Cl- influx = slow down CNS
- Ideal oral sedative for dentistry
- Wider therapeutic index, less addiction potential and less respiratory depression compared to other counterparts
- **Diazepam, Triazolam, Midazolam**

INBDE Pro Tip:
Benzodiazepines can be used for dental oral sedation, as well as for the treatment of seizures.

2. Barbiturates

- GABA receptor agonists
- Contraindicated in those with intermittent porphyria and severe asthma
- Like most sedatives, overdoses can cause respiratory depression
- **Methohexital =** rapid onset, short duration of action, and predictability

Pathophysiology

- Caused by a dopamine deficiency in the brain

3 Parkinson's Disease

- Dopamine is made in the brain from L-DOPA
- L-DOPA has the ability to cross the blood brain barrier (BBB), while dopamine does not
- DOPA decarboxylase is an enzyme that normally breaks down L-DOPA
- **Carbidopa** – blocks DOPA decarboxylase
  - This allows L-DOPA to cross the BBB, so that it can be converted to dopamine once in the brain