2

General Principles of Pharmacology

**KEY TERMS**

- **Affinity**: The force of attraction of a molecule to a receptor site
- **Agonist**: A drug that has a direct stimulatory effect on a receptor
- **Antagonist**: A drug that interferes with the action of an agonist
- **Ceiling dose**: The dose above which no further beneficial drug effect will occur
- **Enteral**: The administration of a drug through the gastrointestinal (GI) tract, by mouth
- **Efficacy**: The magnitude of response obtained from optimal receptor site occupancy by a drug
- **Half-life**: The time it takes for half the drug to be removed from the body
- **Intrinsic activity**: The ability to cause an effect or action
- **Parenteral**: The administration of a drug bypassing the GI tract, usually through injection into the body in various ways but also including inhalation and topical administration
- **Partial agonist**: A drug with affinity for the receptor site, but unable to produce a strong effect or action
- **Pharmacodynamics**: The mechanisms of drug action involving biochemical and physiologic effects of drugs
- **Pharmacokinetics**: The absorption, distribution, metabolism, and excretion of a drug
- **Pharmacotherapeutics**: The use of pharmacologic agents to diagnose, treat, or prevent disease
- **Potency**: The concentration at which the drug elicits 50% of its maximal response, related to the drug’s affinity for the receptor
- **Receptor site**: A specialized area on a cell or within a cell where a drug acts to initiate a series of biochemical and physiologic effects
- **Strong agonist**: Drug that produces a significant physiologic response when only a relatively small number of receptors are occupied
- **Toxicity**: Overdose, undesirable effects, or poisoning

**KEY ACRONYMS**

- **IM**: Intramuscular
- **IV**: Intravenous
- **ROA**: Route of administration
- **SC**: Subcutaneous

The science of pharmacology is the study of drugs. The science developed when early individuals observed the effects of herbs and plant extracts on themselves or others. Historically, the clinician was responsible for information about the sources, physical and chemical properties, and compounding and dispensing of drugs. These activities are now delegated to pharmacologists and pharmacists. Today, the practitioner’s responsibility relates to the clinical application of this knowledge. Oral health professionals must understand basic principles of pharmacology as they apply to drugs used in oral health care as well as other drugs taken by the dental patient. This understanding provides for more efficient communication when explaining drug effects to the patient or when medical consultation is necessary. Important principles include:

- knowing how a drug works, called the mechanism of action;
- the potential adverse (or side) effects (ADEs) that are possible;
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- oral health education information related to drug effects;
- the risks of taking a drug.

These principles apply to all therapeutic agents (including vitamins, herbs, and nutritional supplements) and pertain to a drug’s mechanism of action (pharmacodynamics), the movement of the drug through the body (pharmacokinetics), and potential adverse effects when the drug is taken (pharmaco-therapeutic variables).

Self-Study Review

1. List four principles of pharmacology that the oral health professional must understand in order to provide information on drug effects.

2. Define pharmacodynamics and pharmacokinetics as they apply to drugs.

PHARMACODYNAMICS

Pharmacodynamics is the science of molecular interactions between drugs and body constituents. It relates to the biochemical and physiologic actions of drugs. When a drug is delivered to the tissue cells, it goes through several steps. The first step in initiating a drug-induced effect is the formation of a complex, or bond, between the drug molecule and a cell component called the drug receptor. The receptor site where a drug acts to initiate a series of biochemical and physiologic effects is that drug’s site of action. The molecular event that follows this drug-receptor interaction is called the drug’s mechanism of action. An example of this process is the action of epinephrine in local anesthetic agents. Following the injection of a local anesthetic solution (delivery), epinephrine binds to its receptor on vascular smooth muscle (complex formation) and causes the muscle cell to constrict (drug-receptor interaction), resulting in vasoconstriction (mechanism of action). Most drugs go through a similar process; however, it should be understood that not all drugs produce their effects by interacting with specific receptors. This concept will become apparent as one considers drug action in future chapters. A number of drugs form chemical bonds with small molecules, chelating agents, or metallic cations. A practical example of this type of drug-receptor interaction is the therapeutic neutralization of gastric acid by antacids. Many other drugs act by mechanisms that are not yet understood.

Receptors

Drug receptors are large, highly specialized molecules, which are components of the plasma membrane or are located intracellularly. A single cell may have hundreds of different receptor sites, and a drug may interact with a variety of different receptor types or subtypes, producing different pharmacologic effects. Drug molecules and their receptors must have similar structures (structural specificity), described as “lock and key” complementary fit. Figure 2-1 illustrates the complementary fit and the interaction with different receptors. Only one molecule can bind to a receptor at a time; i.e., two drugs cannot occupy the same receptor at the same time. Receptors have a variety of other features that determine their function, location in the body, relationship to cellular membranes, and binding capacity (Box 2-1), including:

- electrochemical force (either electropositive or electronegative) that functions to attract the drug molecule to the receptor
- the trait of being hydrophilic or hydrophobic to attract or repel a molecule
- are cellular macromolecules

BOX 2-1. Characteristics of Drug Receptors

- Cellular macromolecules
- Location on the cell surface or within the cell
- Hundreds of different receptors on a single cell
- Complementary fit between drug and receptor
- Electrochemical charge
- Hydrophilic or hydrophobic
- Only one drug molecule can occupy a receptor at one time
The drug molecule binds to the complementary receptor and stimulates the receptor to produce a definable pharmacologic response.

**Chemical Bonds**

Drugs attach to or interact with these receptor sites through various types of chemical bonds. These include ionic, hydrogen, and covalent bonds, and van der Waals forces. Hydrogen bonding and ionic bonding are the most common types between drugs and receptors. The bonds are similar in that both involve an electrochemical attraction. These interactions require little energy and are made and broken easily.

**Ionic Bonds**

Ionic interactions occur between atoms with opposite charges. An atom with an excess of electrons imparts a negative charge, which causes an attraction to an atom with a deficiency of electrons. A simple example of this type of interaction is reflected in the attraction between sodium and chloride ions (sodium chloride \( \text{Na}^+\text{Cl}^- \)). Applying the concept to the attraction between drug molecules and receptor sites, a positively charged drug molecule is attracted to a negatively charged receptor site. These bonds are weak and are easily reversed.

**Hydrogen Bonds**

When bound to nitrogen or oxygen, hydrogen atoms become positively polarized and bind to negatively polarized atoms such as oxygen, nitrogen, or sulfur. These bonds are generally weaker than ionic bonds.

**Covalent Bonds**

Covalent bonds are the strongest type of bond between a drug and its receptor, resulting from the sharing of electrons by two atoms. The energy required to overcome such interactions can be so great that the bond is often irreversible. Fortunately, such drug–receptor interactions are not common. A good example of a covalent bond is the complex formed between tetracycline and dentin to produce a permanent discoloration.

**van der Waals Forces**

These nondescript forces contribute to the mutual attraction between organic molecules through a shifting of electron density in or around a molecule that results in the generation of transient positive or negative charges. This provides for a weak attractive force between some drugs and their receptors.

**Attractive Forces Between Drugs and Receptors**

Drug molecules move in constant random motion in the cellular area, binding to receptors and breaking away from receptors. The following forces govern the potential for a complex to form.

**Affinity**

When a drug molecule moves so close to its receptor that the attractive force between them becomes great enough to overcome the random motion of the drug molecule, the drug binds to the receptor. This phenomenon is called affinity. The affinity of a drug for a particular receptor and the type of binding that occurs is intimately related to the drug’s chemical structure. Because two drug molecules cannot occupy the same receptor site at the same time, the drug with the greater affinity will bind more readily to the receptor. Affinity is expressed by its dissociation constant \( (K_d) \), which is the concentration of a drug required in solution to achieve 50% occupancy of its receptors. When two drugs of equal concentrations are competing for the same receptor population, the drug with the greater affinity will bind with more receptors (and stimulate the receptor to cause an action) at any given instant (Fig. 2-2). Thus, a lower concentration of that drug will produce the same level of pharmacologic effect. This means that drugs with good affinity have greater potency, i.e., they require a smaller dose to cause a specific effect. Consequently, potency is related to the affinity of a drug.

Figure 2.2 illustrates that when equal concentrations of two drugs are in equilibrium with the same receptor population (square indentations), the drug with the greater affinity (Drug A) will make a greater number of effective bindings at any given instant. The result is that Drug A is more potent, and a lower concentration of Drug A is required to produce the same level of pharmacologic effect as that produced by Drug B.

**Agonists**

Drugs that have direct stimulatory effects on receptors are called agonists. A strong agonist produces a significant physiologic response when only a relatively small number of receptors are occupied. The ability of an agonist to interact with a receptor and initiate a response is the function of its intrinsic activity. Using these terms in an example, when a small dose of a drug (agonist) produces a desired effect, the drug has good affinity and good intrinsic activity. A weak agonist must be bound to many more receptors to produce the same effect, so a much larger dose of a weak agonist will be required to produce the desired effect—i.e., the drug has lower affinity and/or lower intrinsic activity. A partial agonist has affinity for the receptor, but very low intrinsic activity. Therefore, it will never produce the same effect as a strong agonist or a weak agonist, even when all receptors are occupied. This can be illustrated with the log dose–response of three different drugs with affinity to the same receptors, as shown in Figure 2-3, where a low dose of Drug A (strong agonist) produces a full effect, Drug B (weak agonist) must have a higher dose to reach that effect, and Drug C (partial agonist) never reaches the effect produced by Drugs A or B. An example of the above concept would be the use of 5 mg of morphine to relieve strong pain, compared with 50 mg of meperidine (Demerol) to relieve the same degree of pain.
and further compared with 65 mg of propoxyphene (Darvon), which will not relieve strong pain, no matter how high the dose given. Thus the affinity and the intrinsic activity of an agonist determine efficacy of a drug.

**Efficacy**

Efficacy is the maximum response produced by a drug. It is a state of optimal receptor occupancy by the drug molecules; additional doses would produce no further beneficial effect. This concept is often referred to as the **ceiling dose**. As seen with the affinity of a drug for a particular receptor, the efficacy of a drug is also related to its chemical structure. This concept is referred to as the **intrinsic activity relationship**. The quantification of a specific response elicited by a drug given in a range of doses (5 mg, 10 mg, 50 mg, etc.) is called the graded dose–response relationship. This relationship is expressed visually and mathematically with a dose–response curve. The curve is established by placing the logarithmic value for the dose (or log dose) on the x-axis and the quantified response on the y-axis (Fig. 2-4). The upper plateau of the dose–response curve represents the efficacy or the maximal effect of a drug associated with a specific dose. A good example of this concept is acetaminophen, which has a ceiling dose of about 1,000 mg for pain relief. Taking 2,000 mg in a single dose will not produce greater pain relief and may lead to toxicity (overdose). The lowest dose of a drug that will produce a measurable response is called the **threshold dose**. The dose range of acetaminophen for pain relief is 325 mg to 1,000 mg. Therefore, 325 mg would be the threshold dose of acetaminophen.
tagonism can be either reversible (competitive) or irreversible required for receptor activation by an agonist. Receptor antagonist binding domain) and prevent the conformational change they may bind to an adjacent site (overlapping with the agonist binding domain) and prevent the binding of the agonist, or

Receptor antagonists can bind at the active site (called agonist binding domain) and prevent the binding of the agonist, or they may bind to an adjacent site (overlapping with the agonist binding domain) and prevent the conformational change required for receptor activation by an agonist. Receptor antagonism can be either reversible (competitive) or irreversible (noncompetitive):

- A competitive antagonist binds reversibly to the active site of the agonist and maintains the receptor in its inactive conformation. In other words, it has affinity for a receptor but no efficacy (i.e., it cannot cause an effect). It competes with the agonist for the receptor, and the outcome depends on the degree of affinity of the competitive antagonist compared with the agonist. A competitive antagonist forms a reversible drug-receptor complex, which can be overcome by increasing the dose of the agonist. Consequently, the inhibition is surmountable. In effect, the presence of a competitive antagonist reduces the potency of the agonist. A practical example of this type of antagonism with relevance to dentistry is the reversal of respiratory depression caused by excessive doses of an opioid analgesic (agonist) with naloxone, an opioid antagonist.

- A noncompetitive antagonist binds either to the active site or to an allosteric (adjacent) site of the receptor. It binds to the active site either covalently or with very high affinity, both of which are effectively irreversible. An allosteric noncompetitive antagonist prevents the receptor from being activated, even when the agonist is bound to the active site. In effect, the presence of a noncompetitive antagonist reduces the efficacy of the agonist. Aspirin is a practical example of a noncompetitive antagonist. It irreversibly affects cyclooxygenase, the enzyme responsible for the process that causes platelets to clump together and produce a clot. This reduces clotting and increases the bleeding time. Normal platelet function can be reestablished only by the generation of new platelets in the bone marrow.

Nonreceptor Antagonists

A nonreceptor antagonist may be either a chemical or physiologic antagonist.

Chemical Antagonist

A chemical antagonist may either bind a molecule at some point in the activation pathway or directly inhibit the agonist. A practical example of this type of antagonism with relevance to dentistry is the one produced by local anesthetic agents. They block sodium channels in the activation pathway of chemicals that promote depolarization of nerve fibers. By blocking depolarization, information about tissue damage (in the form of electrical impulses) is not transmitted to the cortex, and the patient will not experience pain.

Physiologic Antagonist

A physiologic antagonist activates pathways that oppose the action of the agonist. An example of this type of antagonism is reflected in the action of epinephrine on blood vessels (vasoconstriction) following an allergic reaction (anaphylaxis) and histamine release. The effect of epinephrine overcomes the effect of histamine (vasodilation) on the same blood vessel, and the vessel becomes constricted.

Mixed Agonist–Antagonists

Mixed agonist–antagonists are drugs that have both agonistic and antagonistic properties. When used alone, such a drug behaves as an agonist. However, when another drug that competes for the same receptor site is administered concurrently,
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the agonist–antagonist will also act as an antagonist. A practical example of an agonist–antagonist is pentazocine, an opioid analgesic; when used alone, it interacts with its opioid receptor to produce analgesia, but it antagonizes the action of other opioid agonists.

Receptor Classification
Receptors are classified according to the type of drug they interact with or according to the specific physiologic response produced by the drug–receptor complex. Receptor sites may also be subclassified by evaluating the effects of different agonists in the presence of a given antagonist. The previous example of using epinephrine to counteract the effects of histamine illustrates this concept. Earlier in this chapter, it was noted that drugs can interact with different receptors. Epinephrine can bind to receptors in the bronchioles of the lungs to cause bronchodilation, and it can bind to different receptors on blood vessels to cause vasoconstriction; hence, one drug interacts with two different receptors and causes two different actions.

Similarly, receptors and receptor subtypes exist for many other agents. The number of any given receptor types or subtypes on a cell also may vary. Certain disease states or drugs taken long term and/or in large doses may increase (up-regulate) or decrease (down-regulate) the number of receptors and provide a degree of adaptability in the face of changing physiologic events. Developing tolerance to a drug so the former dose no longer causes an adequate effect and a higher dose is needed to cause the effect illustrates this concept.

Toxicity
Any drug at a high-enough concentration can produce a toxic effect (overdose). In the context of this discussion, toxicity refers to undesirable effects associated with the administration of therapeutic dosages of drugs. These adverse effects may be:

- An exaggeration of direct effects seen at higher doses. For example, barbiturates may produce sedation, drowsiness, and reduced rate of respiration at therapeutic levels (direct effect), but cause death (exaggerated effect of respiratory depression) at increased dose levels. This is an extension of the intended therapeutic effect of central nervous system (CNS) depression.

- Multiple concurrent adverse, or side, effects occurring at therapeutic dosage levels. For example, the administration of certain antihistamines for hay fever, intended to antagonize histamine action at H1 histaminic receptors in the respiratory system, can also bind to H2 histaminic receptors in the CNS and cause drowsiness. In this case, the drowsiness is a concurrent side effect, not an intended response. ADEs are discussed in detail in Chapter 5.

Median Effective Dose or Lethal Dose
The dose of a drug required to produce a desired response in 50% of the individuals within the same population is the median effective dose (ED50), as shown in Figure 2-6. If death is the measured end point, the ED50 is expressed as the median lethal dose (LD50). A steep dose–response curve indicates a narrow dosage range between minimal and maximal effects. Consequently, the risk for toxic or even lethal dosage levels can be greater because of the narrower dosage range. Similarly, the median toxic dose (TD50) is the dose of a drug that produces a specific toxic response in 50% of the individuals within the same population. These concepts are used during drug development to determine the safety of doses. Fortunately, laboratory animals are used to determine the LD50 in drug research centers! The relative safety of a drug for humans is extrapolated from animal data and clinical data during new drug’s clinical trials.

Therapeutic Index
When evaluating potential therapeutic agents, dose–response curves provide valuable information relative to their safety. The margin of safety of a drug is expressed by the Therapeutic Index (TI). For example, if the slope of the dose–response curve is steep, it indicates a narrow range between dosages that produce minimal and maximal effects, or between a safe dose and a toxic dose (Fig. 2-7). Using the dose–response
1. Define the roles of affinity and intrinsic activity in drug action. Which is related to potency?

2. What is the difference in the effect of a weak agonist when compared to a partial agonist? Identify both in a log dose curve illustration.

3. Describe the relationship of efficacy and the ceiling dose concept.

4. Compare the ceiling dose with the threshold dose.

5. Define ED50 and LD50.

6. What is the formula to determine the TI, and what is the significance of a high number?

7. What is the difference in the effect of a strong agonist when compared to a full agonist? Identify both in a log dose curve illustration.

8. Describe the relationship of efficacy and the ceiling dose concept.

9. Compare the ceiling dose with the threshold dose.

10. Define ED50 and LD50.

11. What is the therapeutic index (TI), and how is it used? What is the formula to determine the TI, and what is the significance of a high number?

**PHARMACOKINETICS**

Pharmacokinetics deals with the movement of drugs through the body. Therefore, pharmacokinetics relates to a drug’s absorption, distribution in the body, including to the site of action; metabolism to prepare the drug for removal from the body; and excretion, where the drug is ultimately removed from the body and its effect is terminated. As drugs progress through these various phases within the body to be delivered to their sites of action and, ultimately, to be eliminated from the body, they must pass through biologic barriers (e.g., cell walls, blood vessels) in various tissues.

**Passage across Biologic Membranes**

To produce an effect, most drugs must pass through cell membranes to gain access to their receptor(s). Passage through biologic membranes affects the amount of the drug that reaches the site of action and influences the time it takes the drug to get to the site of action. The physicochemical properties that influence the movement of drug molecules across biologic membranes are molecular size, lipid solubility, and the degree of ionization (a function of the pH of the environment and pKₐ of the drug). In an acid environment, an acidic drug exists mainly in the nonionized form. Nonionized molecules are lipid soluble and pass through biologic membranes easily. In the same acid environment, a basic drug exists mainly in the ionized form. Ionized drugs are water soluble and must pass through water pores of the biologic membrane or be transported through the membrane by specialized transport mechanisms. These movements are accomplished in a variety of ways.

**Filtration**

Small, water-soluble substances may pass through aqueous channels or water pores in cell membranes by a process known as filtration. Larger water-soluble molecules are in the ionized form and are blocked from moving through small water pore openings. They must rely on specialized transport mechanisms (discussed below) to move through the biologic membrane.

**Passive Diffusion**

Most drugs are weak acids or weak bases, and drug molecules are too large to pass through most aqueous channels. However, as a function of their lipid solubility, the nonpolar (non-ionized) forms of these drugs readily can cross biologic membranes by passive diffusion along a concentration gradient (from high concentration to low concentration) until equilibrium is reached across the membrane. Therefore, nonionized lipid-soluble molecules can easily pass through biologic membranes.

**Specialized Transport Mechanisms**

Large ionized, water-soluble drug molecules require more complex processes to cross biologic membranes. These include facilitated diffusion and active transport mechanisms.

**Facilitated Diffusion**

The concept of facilitated diffusion assumes that the drug forms a complex with a component of the cell membrane on one side. The complex is then carried through the membrane, the drug is released, and the carrier returns to the original surface to repeat the process. Vitamins are known to participate in facilitated diffusion, furnishing the energy to carry large, water-soluble drug molecules across membranes. Facilitated diffusion does not require energy and does not proceed against a concentration gradient. One example is the movement of glucose across cell membranes; it is thought to be facilitated by insulin. Another example is that some water-insoluble substances, such as fat-soluble vitamins (vitamins A, D, E, and K), are engulfed by the cell membrane and are released unchanged in the cytoplasm by a process known as endocytosis, a form of facilitated diffusion.

**Active Transport**

Active transport is the movement of drug molecules across biologic membranes against both a concentration and an electrochemical gradient. This activity requires energy. The
Absorption

Regardless of the process by which a drug moves through biologic membranes, it first must be dissolved in the fluids encircling the cells. For this reason, a drug must have some degree of both lipid and water solubility—water solubility to get it to the cell, and lipid solubility to get it through the cell membrane. Factors that influence the rate of absorption of drugs include

- the degree of ionization and pH of tissues;
- the formulation of the drug (liquid or solid);
- the drug’s concentration (the greater the concentration of a drug, the faster the rate of absorption);
- circulation to the area (the greater the blood flow to tissue, the faster the rate of absorption);
- the area of absorptive surface (the greater the area to which the drug is exposed, the faster the rate of absorption);
- the route of administration (ROA; Box 2-2).

Degree of Ionization

As mentioned earlier, the ionized form of a drug tends to be more water soluble, and nonionized forms tend to be more lipid soluble. Biologic membranes are composed of

- layers of lipid material and proteins that allow for passage of lipid-soluble molecules;
- small openings or water pores that allow for the passage of water-soluble molecules.

Consequently, the nonpolar, nonionized form of a drug will diffuse across biologic membranes more readily than its polar, ionized form. This phenomenon has clinical implications. For example, if the patient is taking an antacid, which increases the pH of the stomach and upper small intestine, the administration of a weak acid (such as aspirin) may result in increased ionization and poor absorption of the aspirin, giving less-than-optimal pain relief.

Formulation of Drug

The form in which a drug is administered can affect the rate of absorption. To illustrate this point, let us consider the form in which a drug is administered to a patient. Aqueous formulations of drugs (such as Alka-Seltzer) do not require time to dissolve after oral administration and, therefore, will cover a wider area of the absorptive surface in the gastrointestinal (GI) tract much faster than a tablet, which must go through stages of a dissolving process. In general, the liquid formulation results in an increased rate of absorption of the drug (and more rapid onset of action) than solid formulations of the same drug.

Enteric Coating

Drugs can be modified in various ways that result in delayed absorption. Enteric-coated formulations delay dissolution of tablets until they have moved from the stomach into the upper small intestine, thereby reducing adverse gastric side effects.

Other Modifications

A strategy involved in formulating intraoral topical agents is to combine them with an insoluble agent. This strategy prevents agents applied to the oral mucosa from dissolving in saliva and being removed (e.g., corticosteroid mixed with an insoluble agent [Kenalog in Orabase]). New doseforms and delivery systems are being developed every day. For example, in 2006 the Food and Drug Administration (FDA) approved the very first inhaled insulin, a drug formerly only administered by injection.

Drug Concentration

Highly concentrated drugs are absorbed faster than the same drugs in low concentrations. Absorption of drugs through skin and mucosa by passive diffusion is proportional to the drugs’ concentration and lipid solubility. This concept is discussed further when ROAs are presented.

Circulation to Area

The greater the blood flow to tissue, the faster the rate of absorption. Organs with significant blood flow include the heart, the GI tract, and the liver. This concept is illustrated in the discussion related to ROAs.

Area of Absorptive Surface

The upper small intestine has a large surface area and is the site of absorption for most orally administered drugs. Drugs
The close anatomical relationship between the liver and the GI tract, and the abundant blood supply of these organs, has important effects on the bioavailability of some drugs. Because the liver is situated between enteric sites of absorption and the systemic circulation, it can profoundly influence the amount of drug in circulation when the drug is administered orally—an action that has been described as the *first-pass effect*. A drug given orally is absorbed mainly in the upper small intestine and enters the splanchnic circulation supplying that mucosa. Rectally administered drugs are absorbed via the lower intestinal mucosa. Within the circulation, the drug molecules attach to plasma proteins, called *albumin*. Drugs bound at various ratios to plasma proteins. When the drug binds at a 90:10 ratio, this means that 90% of the molecules are bound to albumin and 10% exist in an unbound form. Albumin serves to carry the molecule in the circulation to be distributed to the site of action. The protein-bound drug is protected from metabolism as the blood moves through the liver. Drugs that are removed efficiently from the liver during “first pass” will have a low bioavailability. Consequently, only that fraction of the drug that reaches the systemic circulation after first-pass metabolism is bioavailable to its receptor site.

**Parenteral**

Parenteral drugs bypass the GI tract and include various injectable routes, such as intravenous (IV), subcutaneous (SC), intramuscular (IM); inhalation; and topical routes. This ROA is considered to be the most predictable ROA. The IV route provides for accurate and immediate deposition of drugs into the circulation, bypassing the absorption phase. The effect is rapid, with almost immediate onset of action. This route is considered to be the most predictable ROA. The IV route is often used in emergency situations. The dose of injected drugs can be adjusted to the patient’s response; however, once a drug is injected, there is no recall. This makes the IV route less safe than the oral route, where absorption can be more controlled. Sterile formulations of soluble substances and an aseptic technique are required. Local irritation, often referred to as injection site reactions, and damage to the inner blood vessel wall can result in thromboembolic complications (Box 2-5).

**Enteral**

The oral route is also the most unpredictable route because many factors can affect the rate of absorption between the GI tract (Box 2-4).

<table>
<thead>
<tr>
<th>BOX 2-3. Routes of Administration</th>
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<tbody>
<tr>
<td>Enteral</td>
</tr>
<tr>
<td>- oral</td>
</tr>
<tr>
<td>- rectal</td>
</tr>
<tr>
<td>Parenteral</td>
</tr>
<tr>
<td>- various injections</td>
</tr>
<tr>
<td>- inhalation</td>
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<tr>
<td>- topical (sublingual, drops, patches, intrasulcus)</td>
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</tbody>
</table>

The rectal route, which is a form of enteral drug administration, may be useful in young children who have trouble swallowing tablet dose forms, and for unconscious or vomiting patients. However, absorption with this route is unpredictable. When a drug is administered enteral, its rate of absorption into the systemic circulation is influenced by:

- the inherent characteristics of the drug (lipid soluble, water soluble, molecular weight, \( pK_a \), of the drug);
- the pH of the GI tract, which can change the ionization characteristics of a drug molecule;
- the presence of food in the stomach, which slows the rate of absorption because the drug competes for absorption with food components in the GI mucosa;
- gastric motility, which can move the drug through the intestines so fast that it does not have time for complete absorption;
- the degree of splanchnic blood flow (blood flow through intestinal viscera)—i.e., the intestinal visera have a large surface area and significant vascularity;
- patient compliance in taking the prescribed drug regimen.

**First-Pass Effect**

Patients who have trouble swallowing tablet dose forms, and for unconscious or vomiting patients. However, absorption with this route is unpredictable. When a drug is administered enteral, its rate of absorption into the systemic circulation is influenced by:

- the inherent characteristics of the drug (lipid soluble, water soluble, molecular weight, \( pK_a \), of the drug);
- the pH of the GI tract, which can change the ionization characteristics of a drug molecule;
- the presence of food in the stomach, which slows the rate of absorption because the drug competes for absorption with food components in the GI mucosa;
- gastric motility, which can move the drug through the intestines so fast that it does not have time for complete absorption;
- the degree of splanchnic blood flow (blood flow through intestinal viscera)—i.e., the intestinal visera have a large surface area and significant vascularity;
- patient compliance in taking the prescribed drug regimen.
Absorption of drugs through skin and mucosa by passive diffusion is proportional to their concentration and lipid solubility. Drugs' concentrations may be increased for topical products because the skin is a barrier to absorption. Warnings related to applying topical anesthetic agents include:
- limiting the area of application in order to reduce the absorption of these concentrated local anesthetic agents;
- avoiding placement of an occlusive dressing;
- avoiding application over abraded areas or where skin is not intact;
- considering the allergic potential.

Systemic adverse effects can occur if occlusive dressings are placed over the drug or if the drug is applied to abraded or inflamed areas. In these situations, the concentrated drug is absorbed more easily, leading to overdose. For unexplained reasons, the topical ROA is more likely to cause allergic drug reactions.

### Sublingual

Topical application of a drug placed under the tongue is absorbed into the lingual venous system through nonkeratinized mucosa. Because venous drainage from the mouth flows into the superior vena cava, and because of the rich vascularity of the oral area, sublingually administered drugs enter the circulation quickly. This direct absorption also has an advantage over enteric administration because it circumvents the metabolic first-pass breakdown in the liver. Absorption of many drugs is immediate, and this ROA is often used when a rapid response is needed, such as when nitroglycerin is used to treat anginal pain.

### Transdermal Patch

Transdermal delivery systems are designed to provide for a slow, continued release of medication. The patch is applied to the skin, eliminating the need for multiple doses of the drug. Most patches consist of several layers: An adhesive to stick to the skin, a membrane to control the rate of drug release, a reservoir where the drug is placed, and a backing material. The patch is applied to the skin, and the drug is absorbed through the skin. Systemic adverse effects can occur if occlusive dressings are placed over the drug or if the drug is applied to abraded or inflamed areas. In these situations, the concentrated drug is absorbed more easily, leading to overdose. For unexplained reasons, the topical ROA is more likely to cause allergic drug reactions.

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**Self-Study Review**

12. Describe the stages a drug goes through from the time of administration to the elimination of the drug.

13. Compare the features of ionized molecules with those of nonionized forms as the molecule moves through tissues to cause an effect.
14. What is the role of specialized transport mechanisms in moving drug molecules across the membrane? Give an example of a specialized transport vehicle.

15. Identify three factors that affect the absorption of a drug.

16. From where in the GI tract are most drugs absorbed?

17. Describe how taking a drug that alters the pH of the stomach can affect the absorption of a drug.

18. Describe two means to alter a drug’s absorption through modifying the formulation.

19. Identify features of enteral and parenteral ROAs.

20. How does food in the stomach affect drug absorption?

21. Describe how the first-pass effect influences the onset of drug action.

22. List parenteral routes and identify the route used in most emergency situations.

23. What is the most predictable ROA?

24. What are the precautions to follow when using topical agents?

Distribution of Drugs

Drug absorption is a prerequisite for establishing adequate plasma levels. Next, drugs must reach their target organ(s) in therapeutic concentrations to produce effects. Drug distribution is achieved primarily through the circulatory system. In most cases, the therapeutic effect of a drug in tissues correlates well with the concentration in the circulation. Tissues and organs vary greatly in their abilities to absorb various drugs and in the proportion of systemic blood flow that they receive. Highly perfused organs, such as the liver, kidney, heart, and CNS, tend to receive the drug within minutes of absorption. Muscles, most viscera, skin, and fat may require a longer amount of time before equilibrium is achieved. When the patient has excess body fat, those drugs that tend to accumulate in fat are slowly released from these fat stores, which can result in high blood levels when multiple doses of the drug are taken. Redistribution may affect the duration of a drug effect. For example, if a drug of high lipid solubility accumulates rapidly in the brain and then is redistributed to other tissues, the drug effects in the brain are reduced. The distribution of drugs—their ability to cross biologic membranes and leave the vascular compartment, and their pKa. The result is that the fetus becomes medicated along with the mother. This is the reason for the restriction of drugs, except prenatal vitamins, during pregnancy.

Plasma Protein Binding

The capacity of tissues (i.e., muscle and fat) to bind and store drugs increases the tendency of drugs to leave the vascular compartment, but this tendency is counteracted to some extent by plasma protein (albumin) binding of drugs. Plasma protein binding is a nonspecific process. Many drugs compete with each other and with endogenous substances for albumin-binding sites. Plasma protein binding tends to reduce the availability of drugs for diffusion into target organs because, in general, only the free or unbound drug is capable of crossing biologic membranes. Because highly protein-bound drugs cannot leave the circulation, their rate of metabolism and excretion also is reduced. The therapeutic consequence of this phenomenon is taken into consideration when drug dosages are determined. Highly protein-bound drugs, such as aspirin, are also an important mechanism for some drug–drug interactions. When administered concurrently with another drug, highly bound drugs will compete for albumin-binding sites, and the drug with the greatest affinity (e.g., aspirin) will tend to “bump” the other drug off the albumin receptor, effectively increasing its free, unbound form. The increased blood level of the free drug molecules can lead to increased therapeutic and/or toxic effects, even though the drug was administered in therapeutic doses.

Blood–Brain Barrier

The distribution of drugs to the CNS and cerebrospinal fluid is restricted by the blood–brain barrier. However, cerebral blood flow is the only limiting factor associated with highly lipid-soluble, uncharged (nonpolar) drugs.

Placenta as a Barrier

In a pregnant woman, drugs pass across the placenta by simple diffusion (once again, as a function of their concentration in plasma, molecular weight, lipid solubility, pH of the vascular compartment, and their pKa). The result is that the fetus becomes medicated along with the mother. This is the reason for the restriction of drugs, except prenatal vitamins, during pregnancy.

Metabolism

Rarely does a drug enter the body and leave it without modification. A number of organs (liver, kidneys, GI tract, skin, lungs) are capable of metabolizing drugs using a variety of enzymatic reactions. However, the liver contains the greatest diversity and quantity of metabolic enzymes, and the majority of drug metabolism occurs there. The liver preferentially metabolizes highly lipophilic drugs, rendering the drugs in their metabolic state and inactive, although some drug metabolites maintain a degree of pharmacologic activity. The kidneys easily eliminate the metabolite form, which is ionized (water soluble). These enzymatic reactions, classified as Phase I and Phase II processes, are collectively referred to as biotransformation and can alter drugs in four different ways:

1. Convert an active drug to an inactive drug
2. Convert an active drug to an active or toxic metabolite
3. Convert an inactive drug to an active drug
4. Convert an unexcretable (more lipophilic) drug into an excretable (more hydrophilic) metabolite

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Phase I Reactions

A drug’s chemical structure is modified through oxidation, reduction, or hydrolysis, which require very little energy. The most commonly used pathway is the hepatic microsomal cytochrome P450 (CYP450) enzyme system, which oxidizes lipophilic molecules. Some drugs are biotransformed by CYP450-independent oxidation, hydrolysis, or reduction. These reactions are not limited to the hepatic endoplasmic reticulum. A practical example is the hydrolysis of ester and amide local anesthetics and the oxidation of epinephrine, which may be hydrolyzed or oxidized, respectively, at their sites of administration within tissues, thereby limiting their systemic toxicity.

Phase II Reactions

The chemical structure of a drug is modified by conjugation to a large polar endogenous molecule. Some metabolites of Phase I reactions can undergo additional Phase II metabolism. In contrast to a Phase I reaction, Phase II biotransformation almost always results in inactivation of the parent drug. Virtually all Phase II metabolites are pharmacologically inactive.

Cytochrome P450 Induction and Inhibition

The CYP450 enzyme system can be induced to increase drug metabolism or inhibited to reduce the rate of a drug’s metabolism, and it is responsible for many adverse drug–drug interactions. For example, chronic ethanol toxicity induces the metabolism of barbiturates, whereas acute ethanol toxicity inhibits the metabolism of barbiturates. Alcohol and barbiturates are additive CNS depressants. These potential drug–drug interactions are the basis for the “DO NOT DRINK ALCOHOL WITH THIS DRUG” warning on a barbiturate prescription. Other drugs (erythromycin, omeprazole, cimetidine, ciprofloxacin) inhibit CYP450 enzymes and decrease the metabolism of many other drugs. This increases the drugs’ blood levels and effectively increases their therapeutic and/or toxic effects.

Excretion

Renal excretion is the most common and important mechanism of drug elimination from the body. Biotransformation prepares the molecule, and the kidney eliminates it via urination. Consequently, following biotransformation, drugs are intrinsically hydrophilic (ionized) and are excreted more readily than lipophilic (nonionized) compounds. A relatively small number of drugs are excreted primarily in the GI tract via the bile, and only minor quantities are excreted through respiratory (exhalation) and dermal routes (perspiration). Lactation is responsible for minor amounts of drug excretion.

Glomerular Filtration, Tubular Secretion, and Reabsorption from the Tubular Lumen

Renal blood flow represents about 25% of total systemic circulation. Therefore, afferent arterioles in the kidney constantly bring free, unbound, and plasma-protein-bound drugs into the glomeruli. The glomerulus is the primary location for drug elimination to occur. Typically, only the free drug is filtered by the glomeruli. A drug may be filtered at the renal glomerulus or secreted into the proximal tubule, and, subsequently, either may be reabsorbed into the tubular lumen and returned to the circulation or may be excreted into the urine where, via urination, it is removed from the body (Fig. 2-8).

The mechanism includes these processes:

- Glomerular filtration depends on renal blood flow, glomerular filtration rate, and plasma protein binding. Reduced renal blood flow, reduced glomerular filtration rate, and increased plasma protein binding all contribute to reduced drug elimination.
- Active tubular secretion facilitates the movement of the drug from the bloodstream into the renal tubular fluid by a nonsaturating carrier system for organic ions. Some drugs, such as penicillin, aspirin, and probenecid, are actively secreted at the proximal tubule and compete with each other for the same secretory transport mechanisms.
- Passive tubular reabsorption of nonionized drugs results in net passive reabsorption. Although reabsorption can decrease the elimination rate of drugs, many drugs exhibit pH trapping in the distal tubules and are efficiently eliminated in the urine. When drugs need to be retained in the body, the pH of the urine can be manipulated. By alkalinizing the urine (via administration of sodium bicarbonate), the plasma level of weak acids can be decreased; alternatively, by acidifying the urine (via administration of ammonium chloride), the plasma level of weak bases can be decreased.

In summary, drug molecules are removed from the circulation into renal proximal tubules by the glomeruli, or they may be secreted into renal proximal tubules from peritubular capillaries and, if not reabsorbed in the collecting tubules of the kidney, excrated in the urine. Although the kidneys excrete most drugs via glomerular filtration, there are other mechanisms whereby the body eliminates drugs.

Enterohepatic Recirculation

Some metabolites formed in the liver are excreted via the bile into the intestinal tract to be eliminated in the feces. If these metabolites are subsequently hydrolyzed and
reabsorbed from the gut (a process called enterohepatic recirculation), drug action can be re-established. One could say this is the body’s contribution to recycling! Enterohepatic recirculation can result in a significant delay in the elimination of drugs from the body.

Exhalation

Pulmonary excretion is important mainly for the elimination of anesthetic gases and vapors.

Other Mechanisms

Drugs can be excreted in lactation and are potential sources of unwanted pharmacologic effects in nursing infants. Other routes, such as saliva, sweat, and tears, are quantitatively unimportant.

Half-Life of a Drug

The removal of most drugs from the body follows exponential or first-order kinetics. Assuming a relatively uniform distribution of a drug within the body (considered to be a single compartment), first-order kinetics implies that a constant fraction (%) of the drug is eliminated per unit time. The rate of exponential kinetics may be expressed by its constant (k), the fractional change per unit time, or its half-life (expressed as $t_{1/2}$), which is the time required for the plasma concentration of a drug to decrease by 50%. This occurs in several ways, such as:

- the distribution half-life, which represents the rapid decline in plasma–drug concentration as 50% of the drug is distributed throughout the body;
- the elimination half-life, which reflects the time required to excrete 50% of the drug from the system.

Following the administration of multiple therapeutic dosages of a drug at time intervals equal to or shorter than the drug’s half-life, a plateau level of drug accumulates. This is called steady-state concentration and involves over four half-lives. For example, if the $t_{1/2}$ of a drug is 1 hour, then it will require the administration of four therapeutic doses at 1-hour intervals to reach steady state (Fig. 2-9). The plateau represents a rate of drug administration that is equal to the rate of drug elimination. Consequently, fluctuations in the plasma concentration of drugs occur as a function of the dosage interval and the drug’s elimination half-life. Assuming first-order kinetics, it takes approximately four half-lives to eliminate a drug from the body. The elimination of some drugs (such as alcohol) may follow zero-order kinetics, implying that a constant amount of the drug is eliminated per unit time. In this case, the enzymes that metabolize the drug become saturated and cannot absorb more drug, resulting in a constant amount of drug being metabolized per unit of time. Small changes in the dose of drugs with this type of kinetics can lead to large serum concentrations and increase the risk for toxicity.

**Self-Study Review**

25. Describe features of distribution that affect a drug molecule reaching the receptor.
26. What is the role of albumin in the blood?
27. Identify the organ responsible for most drug metabolism.
28. Describe the four ways drugs are altered during biotransformation.
29. What are the differences between Phase I reactions and Phase II reactions in biotransformation?
30. Which enzyme system is the primary pathway for drug metabolism?
31. In which organ are most drugs excreted? What is the primary area of the organ where this occurs?
32. Describe the process of drug excretion.
33. Define a drug’s half-life.

**CONCLUSION**

After initial administration of a drug, there is a period of time before any perceptible effect of the drug is observed in the patient. The time of onset is determined mainly by the rate and degree of absorption. The effect increases with time until the drug reaches the peak effect. Movement through biologic membranes and drug redistribution influences the peak effect. The effect diminishes as the drug is metabolized and eliminated from the body. The duration of action is affected primarily by the rate of inactivation and excretion of the drug by the liver and kidneys. The onset of action, the peak effect, and the duration of action are all dependent upon the dose administered—i.e., the larger the dose, the shorter the time to reach the peak effect, and the longer the duration of action. An important clinical use of time-effect relationships involves multiple dosing schedules over a period of time that depends on the drug’s half-life. To minimize adverse events, the dosage schedule must be designed to avoid giving more drug than has been eliminated since the last dose.
### CLINICAL APPLICATION EXERCISES (CAE)

| Exercise 1. | During the review of the health history, it is noted that the patient lists Tums as a current over-the-counter (OTC) medication. The current appointment is for periodontal débridement of one quadrant. The diagnosis of the case is severe chronic periodontal disease, and a recommendation will be made for “saltwater rinse in evening, plus OTC medication for pain relief.” How will the current drug history information affect your recommendation for pain relief? |
| Exercise 2. | During oral examination, your patient gasps, clutches his chest, and cries out in pain. He reports taking anticholesterol medication due to a recently identified problem with high cholesterol. You tell the receptionist to call 911, and you secure the medical emergency kit. What ROA should be used to get the vasodilating drug to the coronary arteries quickly? |
| Exercise 3. | Your patient is an elderly, overweight person who presents to the office in pain. The dentist decides to prescribe a narcotic agent. What considerations are important in determining dosage, and why? |