2 Principles of Pharmacology

Laura Williford Owens, Robin Webb Corbett, Tekoa L. King

© Sofnamming/Shutterstock

Chapter Glossary

Absorption Movement of drug particles from the gastrointestinal tract to the systemic circulation by passive absorption, active transport, or pinocytosis.

Affinity Degree of attraction between a drug and a receptor. The greater the attraction, the greater the extent of binding.

Agonist Drug that activates a receptor when bound to that receptor.

Agonist–antagonist Drug that has agonist properties for one opioid receptor and antagonist properties for a different type of opioid receptor.

Allele One of a number of alternative forms of a gene or DNA sequence that is located at a specific position on a specific chromosome. Each individual inherits two alleles for each gene. If the two alleles are the same, the person is homozygous. If they are different versions of the gene, the person is heterozygous. Genes can have several different forms or different alleles.

Antagonist Drug that prevents a receptor from being activated when bound to that receptor.

Bioavailability Percentage of an administered drug that is available to the target tissues.

Bioequivalence State in which a product's bioavailability falls within 80% to 125% of the bioavailability of the reference drug. If two products are bioequivalent, one can usually be substituted for the other.

Biotransformation Chemical changes a substance undergoes in the body.

Blood–brain barrier Characteristics of the capillaries surrounding the brain that create a natural barrier to the exchange of drugs between the systemic circulation and the circulation in the central nervous system.

Chronobiology (chronopharmacology) Use of knowledge of circadian rhythms to time administration of drugs for maximum benefit and minimal harm.

Clearance Measure of the body's ability to eliminate a drug.

Competitive antagonist Drug or ligand that reversibly binds to receptors at the same receptor site that agonists use (active site) without activating the receptor to initiate a reaction.

Cytochrome P-450 (CYP450) Generic name for the family of enzymes that are responsible for most drug metabolism reactions.

Dissolution Disintegration of solid drugs (tablets) into small particles in the gastrointestinal tract so that they can dissolve into a liquid.

Distribution Process by which a drug becomes available to body fluids and body tissues.

Dose–response relationship (dose–response curve) Change in the response to a drug caused by different doses of that drug. Dose–response curves help determine safe doses for drugs.

Drug–drug interaction Altered drug effect that occurs when another drug is administered at the same time or in close proximity to the original drug's administration time.

Drug–herb interactions Altered drug effect that occurs when certain herbs are taken at the same time or in close proximity to a drug's administration time.

Drug–nutrient interaction Altered drug effect that occurs when certain foods or liquids are taken at the same time or in close proximity to a drug's administration time.

© Jones & Bartlett Learning, LLC. NOT FOR SALE OR DISTRIBUTION.

Efficacy Capacity to induce a therapeutic response. As opposed to effectiveness, which is the ability of a drug to produce a therapeutic response in real life conditions.

Elimination Removal of a drug or its metabolites whereby the drug or metabolites are changed to a water-soluble form, and thereby removed via the kidneys; less common elimination routes include liver, bile, feces, saliva, lungs, sweat, and breast milk.

Enteric coating Drug coating applied to slow the release and absorption of a drug in the stomach.

Excretion Elimination of a drug from the biologic system.

Extended release (sustained release, slow release) Drug designed to be released over an extended period of time.

First-pass metabolism (first-pass effect) Drug metabolism that occurs as a drug passes through the intestinal lumen, portal vein, and liver prior to entering the systemic circulation. Also known as hepatic first pass.

G-protein–coupled receptor Type of cell membrane receptor. The drug binds with this receptor, which then binds with guanosine triphosphate (GTP) and activates an effector (enzyme) in the cell.

Half-life Time it takes for half of the drug concentration to be eliminated from the body ($t½$).

Hydrophilic Drug that is water soluble. A drug or drug metabolite must be hydrophilic to be excreted in urine.

Inducer Drug that stimulates production of one of the CYP450 enzymes, which in turn rapidly metabolizes the substrate drug. This can results in a decreased therapeutic effect of the substrate drug.

Inhibitor Drug that prevents production of a CYP450 enzyme, which in turn decreases metabolism of the substrate drug. This results in an increased plasma level of the substrate drug and, therefore, an increased therapeutic effect, adverse drug reaction, and/or toxic effect.

Inverse agonist Drug that binds to receptors that have an intrinsic or basal activity, which results in antagonism of this basal activity and downregulation of the receptor's effect. Antihistamines are inverse agonists.

Ligand Drug or chemical that binds to a specific receptor.

Lipophilic Drug that has a high affinity for fat. Lipophilic drugs transfer readily across the phospholipid cell membrane.

Loading dose Administration of a large initial drug dose.

Maximum effect Maximum drug effect; it varies by drug.

Metabolism Change of a drug, primarily in the liver by CYP450 enzymes, into metabolites that may be pharmacologically active or inactive. Drug metabolism alters a drug so that it may be eliminated.

Minimum effective concentration Minimum concentration of a drug in serum required to produce a desired pharmacologic effect.

Narrow therapeutic index As defined by the Food and Drug Administration, less than a twofold difference between the median effective dose and the median lethal dose.

Noncompetitive antagonist Drug or ligand that reversibly binds to a receptor at a site different from the active site used by agonists; this binding causes a structural change that inhibits the agonist from binding to the active site. Noncompetitive antagonists do not compete for the active binding site but they do have an antagonist effect.

Partial agonist Drug molecule that elicits a partial pharmacologic response.

Peak level Highest plasma drug concentration.

P-glycoprotein Permeability glycoprotein (P-gp); a transmembrane protein that serves as a drug transporter and moves drugs out of cells. Also known as multidrug resistance protein 1 (MDR1) or ATP-binding cassette subfamily B member 1 (ABCB1).

Pharmacodynamics Study of drug concentration and the recipient's response; the study of a drug's effects, including the duration and the magnitude of the response in relationship to the drug dose.

Pharmacokinetics Process of drug absorption, distribution, metabolism, and elimination.

Phase I reaction First half of enzymatic metabolism, which makes a drug water soluble so it can be excreted; it includes oxidation, hydrolysis, and/or reduction reactions.

Phase II conjugation reaction Second half of the drug metabolism process, which makes the drug polar and finalizes the changes that make it water soluble.

Polymorphism One of two or more naturally occurring variants of a particular DNA sequence on a chromosomal locus. The DNA variant is termed a polymorphism (as opposed to a mutation) when it appears in more than 1% of a population. Two types of polymorphisms are distinguished: insertions/deletions and single-nucleotide polymorphisms (SNP) wherein there is a change in the order of an amino acid base.

Polypharmacy Concurrent use of many different drugs and/or excessive use in excess of that which is clinically recommended.

Potency Concentration at which a drug elicits 50% of its maximal response.

Prodrug Biologically inactive or partially active drug that is changed as a result of the body's metabolism into an active drug.

© Jones & Bartlett Learning, LLC. NOT FOR SALE OR DISTRIBUTION.

Protein binding Fraction of total drug in the plasma that is bound to plasma proteins.

Receptor Protein or molecular complex that, when bound to a ligand (drug), either initiates a physiologic response or blocks the specific response that the receptor normally stimulates.

Steady state When drug elimination equals drug availability. Average concentration of the drug remains constant when it reaches a steady state.

Therapeutic effect Desired physiological or psychological response to a drug.

Therapeutic equivalence State in which two different drugs are pharmaceutically equivalent (contain the same active ingredient at the same dose) and have the same clinical effect with regard to both safety and efficacy when administered under specified conditions. The FDA has criteria for determining therapeutic equivalence.

Therapeutic index Guideline that estimates the margin of safety of a drug through the use of a ratio that measures the effective dose in 50% of the population and the lethal dose in 50% of the population.

Therapeutic range (therapeutic window) Plasma drug concentration between the minimum effective concentration in the plasma for obtaining the desired drug action and the mean toxic concentration.

Volume of distribution Relationship between the dose of the drug administered and the serum concentration after administration.

Xenobiotic Chemical found in an organism that is not normally produced or expected to be present. Drugs can be xenobiotics, but the term is more frequently used to refer to toxins and poisons.

Introduction

During a typical lifespan, the average woman will take numerous medications, including prescription and nonprescription agents, and perhaps some natural medicinal substances such as herbs or other dietary supplements. These chemicals, via their action on physiologic processes, can be used to produce therapeutic benefit but can also cause toxic effects. This chapter reviews basic pharmacologic principles as applied to women's health.

The Nature of Drugs

Before a drug can elicit a physiologic response, it must be absorbed into the body and transported from a site of administration to the site of action. In most cases, the chemical (or drug) interacts with a specific target or **receptor** in the biologic system. There are several different types of receptors in the body. Many of them are located on the cell membrane (Figure 2-1). For a drug to possess the ability to produce medical benefits, it must have the appropriate size, electrical charge, shape, and composition to interact with a receptor and produce an effect. Interestingly, most receptors in the body exist naturally as targets for endogenous chemicals such as epinephrine, serotonin, or estrogen. Thus, drugs used for pharmacologic purposes often have some structural similarity to chemicals made naturally within the body. In addition, the drug should be able to leave the biologic system through elimination or inactivation in a reasonable amount of time so that the drug's actions are not inappropriately long or permanent.

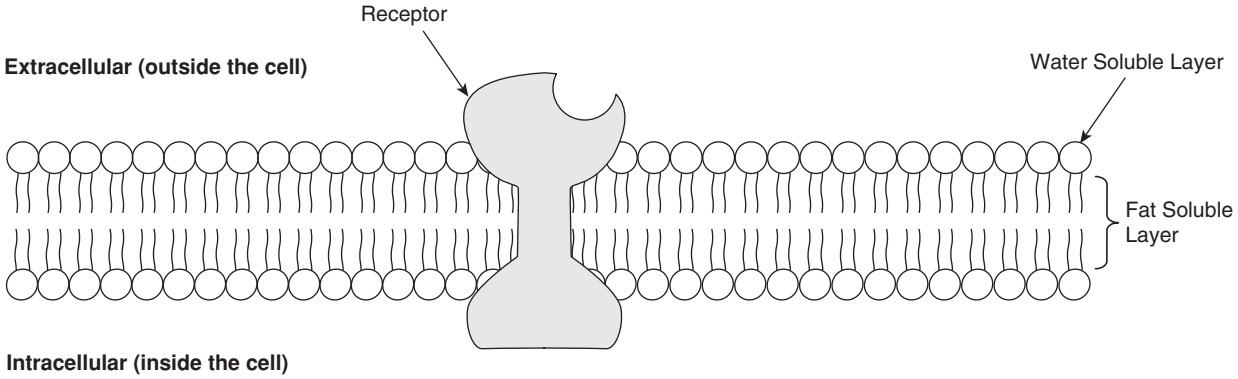


Figure 2-1 Cell membrane receptor.

© Jones & Bartlett Learning, LLC. NOT FOR SALE OR DISTRIBUTION.

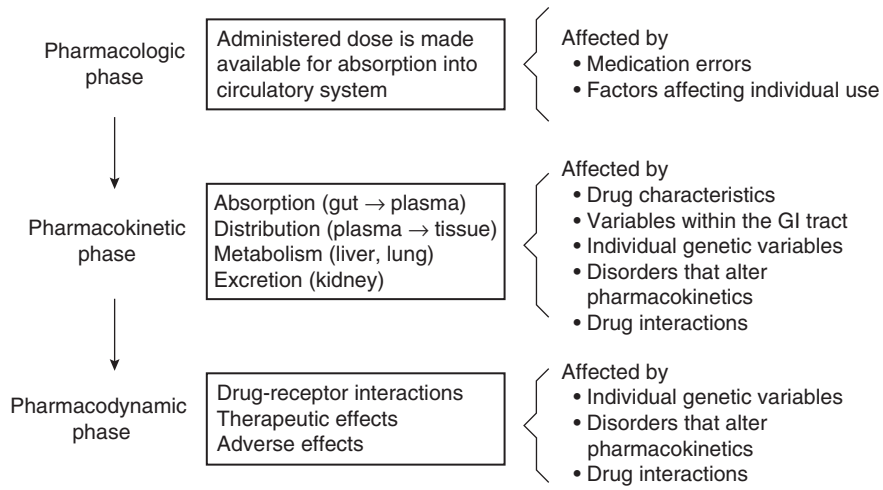


Figure 2-2 Factors that determine the intensity of drug responses.

Drugs can be solid, liquid, or gaseous at room temperature. This physical nature of the chemical often determines the best route through which the drug should be administered. Examples of routes of administration include intravenous (IV), intramuscular (IM), subcutaneous (SQ), inhalation, and transdermal (TTS), as well as enteral administration, such as oral (PO), rectal (PR), and sublingual (SL). Routes of administration vary depending on the physiochemical properties of the drug, including its molecular weight, fat or water solubility, and degree of ionization. Additionally, the route of administration affects the speed of absorption. Different routes may require various doses and dosage forms.

In considering all of the aforementioned factors, it is difficult to conceptualize how safe and effective drugs are developed and utilized for beneficial effects in the human body. The multitude of changes a drug undergoes between its administration and its stimulation of the intended response are divided into two major categories. **Pharmacokinetics** refers to the changes that a drug undergoes during its course through the body. **Pharmacodynamics** refers to the physiologic effects that the drug has on body function (Figure 2-2).

Pharmacokinetics

Pharmacokinetics specifically focuses on the kinetics of drug **absorption**, **distribution**, **metabolism**, and **excretion**. Clinical pharmacokinetics incorporates known pharmacokinetic principles of drug absorption, distribution, metabolism, and excretion but is based on the woman's disease state and takes into consideration individual-specific factors. A common example is when a laboratory measures a person's serum or plasma drug level. This numerical value is combined with knowledge of the disease state and conditions that influence the distribution of that particular drug. Kinetic principles can then be applied and used to modify the drug dose and subsequent drug serum levels to produce desirable changes in the individual's disease state. Examples of drugs for which serum plasma levels are drawn for clinical decision making include magnesium sulfate, vancomycin (Vanocin), theophylline (Theo-Dur), phenobarbital (Luminal), lithium (Lithobid), and digoxin (Lanoxin).

Absorption

After a drug is administered, it should be able to reach its intended site of action. This requires that the drug be absorbed into the circulation from its site of administration (Table 2-1).[1] Drugs can be absorbed via passive diffusion, active diffusion, or pinocytosis. Most drugs rely on passive diffusion. When a drug has a structure similar to a physiologic compound that moves across cell membranes via active transport, it is likely to be transported via active transport as well. Penicillin, for example, moves into the circulatory system via active transport. Macromolecules such as insulin and drugs made of large proteins access the circulatory system via pinocytosis.

© Jones & Bartlett Learning, LLC. NOT FOR SALE OR DISTRIBUTION.

Table 2-1 Absorption Speed of Various Drug Formulations

Type of Formulation	Absorption Rate
Oral Formulations	
Liquids, syrups, and elixirs	**Fastest**
Suspensions	
Powders	
Capsules	
Tablets	
Coated tablets	
Enteric-coated tablets	**Slowest**
Parenteral Formulations	
Intravenous (IV)	**Fastest**
Intramuscular (IM)	
Subcutaneous (SC)	
Intrathecal (IT)	
Epidural	**Slowest**

Source: Data from Guittierrez K. *Pharmacotherapeutics.* 2nd ed. St. Louis: Saunders Elsevier; 2008: 44.[1]

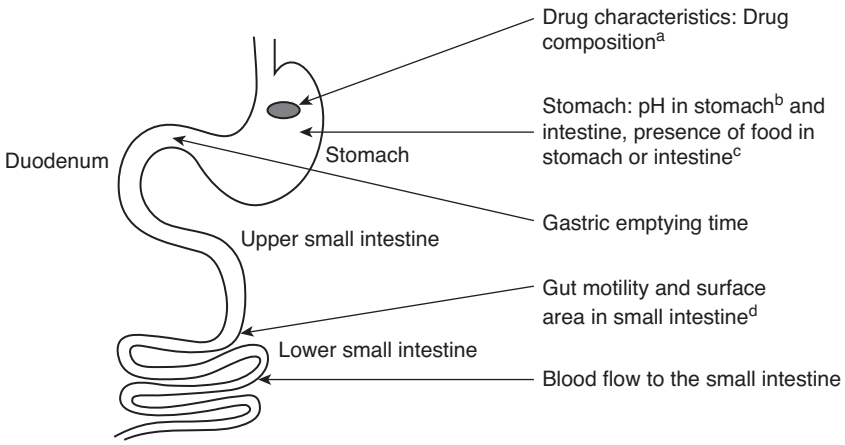
Role of pH

Most drugs are weak organic acids or bases that exist in either an ionized or un-ionized form. Acidic drugs are in an un-ionized form that is lipid soluble or **lipophilic**; as a consequence, they diffuse easily across the phospholipid bilayer cell membrane. Basic drugs are in an ionized form and are water soluble or **hydrophilic**. These drugs cannot pass through the cell membrane into the intracellular compartment easily. The pH in the gastrointestinal tract also affects this process because the proportion of a drug that is un-ionized or lipophilic depends on the pH of the environment. The stomach is acidic with a low pH, and drugs that are weak acids are mostly in their un-ionized form in an acidic environment. Therefore, weak acids such as aspirin will readily be absorbed in the stomach. Conversely, the pH in the small intestine is more basic, and weak bases are more likely to be in their un-ionized form in this environment.

Oral Administration

Administering drugs orally is the preferred route of administration because it is safe, inexpensive, and convenient compared to other routes. Orally administered drugs (typically in tablet or capsule forms) must disintegrate into smaller particles, dissolve in the gastric fluid, and pass across the cell membranes within the gastrointestinal (GI) tract to be absorbed into the circulation. In addition, passage through the GI tract must alter the chemical characteristics of drugs that rely on passive diffusion so they become un-ionized and lipid soluble.

The oral route of administration does possess some disadvantages (Figure 2-3). Some drugs have limited absorption secondary to how their chemical characteristics respond to the environment of the GI tract, including the low pH of gastric acid, destruction by gastric enzymes, differences in gastric emptying rates, and



[a]Various aspects of the drug's chemical characteristics will affect absorption. For example, enteric coating will slow absorption, and drugs that are lipid-soluble will be absorbed more rapidly.

[b]Presence of antacid in the stomach will change the pH. This increases absorption of basic drugs and decreases absorption of acidic drugs.

[c]Food that is in the stomach or intestine can either facilitate or interfere with drug absorption.

[d]The small intestine has the greatest surface area, which is why most drugs are absorbed in the small intestine.

Figure 2-3 Factors that affect absorption of drugs.

© Jones & Bartlett Learning, LLC. NOT FOR SALE OR DISTRIBUTION.

adverse drug reactions such as vomiting due to gastric irritation. Infants and older individuals have less gastric acidity, which, in general, decreases drug absorption. The effect of food that is present in the GI tract also influences the absorption of drugs, albeit in a very drug-specific manner.[1] Some drugs are best taken with food to minimize gastrointestinal irritation, whereas other drugs' absorption may be impeded by food. Also, specific foods may enhance drug absorption.

Some drugs have an **enteric coating** that is intended to prevent the drug's disintegration and absorption in the stomach with subsequent absorption in the less acidic small intestine. In addition, **extended-release** (also known as **sustained-release** or **slow-release**) drugs may have multiple compressed coatings to allow release of the drug over time. These preparations are designed to produce slow, uniform absorption of the drug for 8 hours or more. The advantages of the coated preparations compared to their immediate-release counterparts include longer dosing intervals, maintenance of a therapeutic effect for a prolonged period of time, and decreased incidence and/or intensity of both undesired effects and nontherapeutic blood levels of the drug. Often, these drugs are designated by abbreviations such as *CR* (controlled release), *LA* (long acting), or *SR* (sustained release). To add to this confusion, "extended release" is the term recommended by the U.S. Pharmacopeia, but extended-release formulations can be labeled *XL*, *XR*, or *ER* depending on the choice of the pharmaceutical company that markets the drug.[3] These formulations should not be crushed, chewed, or scored (broken).

First-Pass Metabolism

After an orally administered drug enters the body, it passes through the intestine, intestinal wall, the portal blood system, and the liver before it enters the systemic circulation. Most drugs undergo metabolic changes during this trip via their interaction with (1) bacterial enzymes in the intestine; (2) permeability glycoprotein, usually referred to as **P-glycoprotein** (P-gp), which is a multidrug efflux pump present in the brush border membrane of gastrointestinal cells; (3) cytochrome 450 enzymes (CYP450 enzymes) present in gastrointestinal cells; and (4) CYP450 enzymes in the liver. Drug metabolism is called **biotransformation** because the structure of the drug is altered chemically. The biotransformation that occurs before the drug enters the systemic circulation is referred to as **first-pass metabolism** or the **first-pass effect**.[4,5]

As a result of first-pass metabolism, a proportion of the drug dose fails to enter the systemic circulation, thereby reducing the drug's bioavailability (Figure 2-4). Estrogen, for instance, is extensively metabolized in the liver via the first-pass effect. Alternative routes of administration for estrogen compounds such as patches and vaginal rings have been devised to decrease the amount of drug that must be administered to accommodate the first-pass effect.

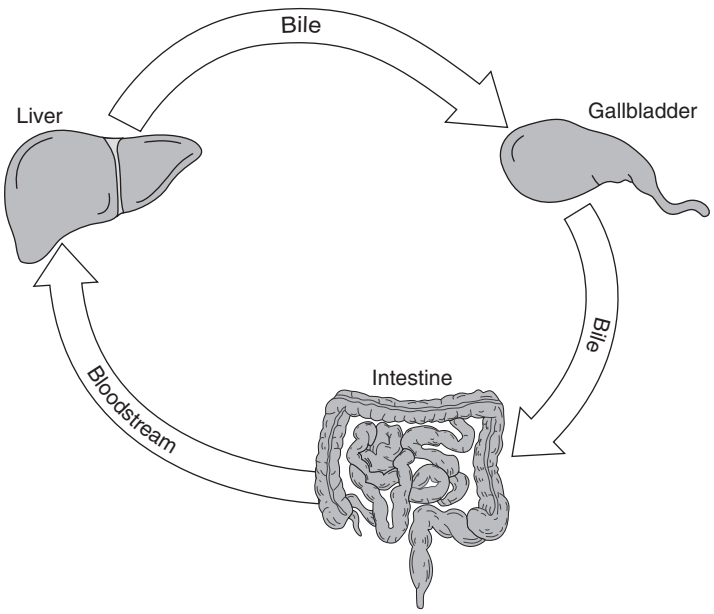


Figure 2-4 Hepatic first-pass metabolism.

© Jones & Bartlett Learning, LLC. NOT FOR SALE OR DISTRIBUTION.

Role of Enterohepatic Circulation

Some drugs are recycled through the enterohepatic circulation. When this occurs, there is an increased risk that their toxic effects will be manifested.[6] Once these drugs enter the liver and are taken up by hepatocytes, they are excreted into bile either unchanged or as metabolites. After the bile enters the gastrointestinal tract, the excreted drug is reabsorbed into the hepatic circulation, which can result in another peak in the plasma concentration of the drug or hepatotoxicity.

In summary, determinants of drug absorption following oral administration include properties that affect **dissolution** such as dosage forms, pH in the stomach and small intestine, and the size of the tablet. The next determinant is gastric emptying time, which is affected by the presence of food, antacids, or other drugs, as well as disease processes that might exist in the GI tract. Intestinal motility then affects the amount of time a drug is presented to the gastric lumen cells and, occasionally, the time available for drug degradation by microflora in the gut. Next, chemical properties of the drug such as water versus lipid solubility affect drug passage through the intestinal endothelial cells, and some drugs are metabolized by the intestinal endothelium or partially returned to the intestinal tract by P-gp. Finally, the extent to which a drug is metabolized via the first-pass effect will dictate the dose that must be used for oral administration.

Parenteral Administration

Drugs administered by parenteral routes (intravenous, subcutaneous, or intramuscular) bypass the GI tract, which allows for a more rapid, extensive, and predictable drug absorption as compared to other routes of administration. In the case of subcutaneous and intramuscular administration, the drug creates a depot under the skin and is absorbed into the systemic circulation by simple diffusion. The rate of absorption for these routes is limited by the area of the absorbing capillary membranes and by the solubility of the substance in the interstitial fluid. A subcutaneous injection can be used only for drugs that are not irritating to tissue; otherwise, severe pain, necrosis, and tissue sloughing may occur. The rate of absorption following subcutaneous injection of a drug often is sufficiently constant and slow to provide a sustained effect. This slow and constant rate is used and altered intentionally, as in the case of insulin: Altering the particle size, protein complex, and pH can provide for short (3–6 hours), intermediate (10–18 hours), and long-acting (18–24 hours) preparations of this hormone.

Drugs in aqueous solution are absorbed rapidly after intramuscular injection. This rate can be altered if the rate of blood flow surrounding the injected area is increased, as can happen during local heating (e.g., a hot bath), massage, or exercise. All of these measures increase vasodilatation, which in turn increases drug absorption into the systemic circulation. A slow, constant absorption from the intramuscular site can be achieved if the drug is injected in solution in oil vehicles; indeed, antibiotics are often administered in this manner.

Because intravenous administration injects the drug directly into the systemic circulation, 100% bioavailability is achieved. No first-pass effect occurs, and there are no barriers (e.g., skin) to drug absorption with this route. The drug delivery is controlled and achieved with an accuracy and immediacy not possible by the other routes. Drugs that cannot be administered intravenously include drugs in an oily vehicle, drugs that precipitate blood constituents or hemolyze erythrocytes, and drug combinations that result in the formation of precipitates.

Sublingual Administration

Sublingual administration occurs when a drug is placed under the tongue and absorbed into the blood. For some drugs, the sublingual route can be a convenient route of administration that bypasses the first-pass effect. The venous drainage from the mouth is to the superior vena cava, which protects the drug from rapid first-pass metabolism. Nitroglycerin is administered via sublingually because it is absorbed rapidly through this route; in contrast, if administered orally, it undergoes extensive metabolism by the liver until it reaches the point at which it essentially is removed from the circulation.

Transdermal Administration

Transdermal administration refers to the administration of a drug molecule through the skin for absorption into the circulation. Transdermal preparations are developed to deliver a consistent drug dose over a day or a period of days. Not all drug molecules can readily penetrate intact skin, but when they are able to do so, the amount absorbed depends on the surface area over which the drug is applied and on lipid solubility (the epidermis behaves as a lipid barrier). Transdermal administration can be convenient for some individuals, and this dosage form has become more popular in recent years. Controlled-release topical patches that have become increasingly available include nicotine for tobacco-smoking withdrawal, scopolamine (Transderm-Scop) for

© Jones & Bartlett Learning, LLC. NOT FOR SALE OR DISTRIBUTION.

motion sickness, nitroglycerin for angina pectoris, estrogen (e.g., Vivelle, Climara, Estraderm) for menopausal therapy, and estrogens plus progestins for contraception. Systemic absorption of drugs occurs much more readily through abraded, burned, or denuded skin because the dermis is freely permeable. Also, when the skin is inflamed (causing an increase in cutaneous blood flow), drug molecules can more easily pass through the skin layer. Toxic effects can occur if highly lipid-soluble drug molecules are applied to skin that is not intact, so one must avoid transdermal administration in this situation. Conversely, lotion and ointments on the skin tend to impair drug transfer through transdermal administration.

Rectal Administration

When a drug is administered rectally, the drug molecule either is absorbed into the systemic circulation or placed to induce a localized effect, as in the case of hydrocortisone suppositories for hemorrhoids. This route of administration can be the preferred route when the individual is nauseated, vomiting, or unconscious. The potential for first-pass metabolism is less than that noted with the oral route of administration because approximately 50% of the drug that is absorbed from the rectum will bypass the portal system. However, rectal absorption often is irregular and incomplete, and many drugs can cause irritation of the rectal mucosa.

Pulmonary Administration

Some drugs are inhaled and subsequently absorbed through the pulmonary epithelium and mucous membranes of the respiratory tract. Systemic absorption of drug molecules through this route is typically rapid due to the lungs' large surface area. Advantages of this route of administration include rapid absorption of a drug molecule into the blood, avoidance of first-pass metabolism, and local application of the drug at the desired site of action in the case of pulmonary disease such as asthma. Inhaled drugs are often administered by nebulizer or a metered-dose inhaler that can create aerosols of small particles. For example, albuterol (Proventil HFA) may be administered by inhaler for individuals experiencing an acute asthma attack. More than one treatment may be required, depending on the severity of the attack and the person's response to the drug.

Topical Administration

When the drug is intended for local action (e.g., administration of eye drops for glaucoma), it is administered topically. Drug absorption through this route is continuous, although it has a slower onset of action. Systemic absorption is unlikely but does increase if the drug molecule is applied to mucous membranes. Drugs given via topical administration include ophthalmic drugs, which may take the form of drops or an ointment; erythromycin ointment (Ilotycin), for example, often is administered to newborns in the first few hours after birth to prevent ophthalmic neonatorum. Likewise, otic drugs (ear drops) may be given via topical administration to treat infections or to facilitate removal of cerumen. Both ophthalmic and otic drugs require diligence in identifying the correct eye/ear for administration, appropriate positioning of the individual for drug administration, and administration techniques specific to the drug medium.

In summary, factors that affect absorption are important considerations for the clinician because the drug must reach its intended site of action before it can begin to produce a change in the biologic system. However, in the end, the clinician is primarily concerned with bioavailability rather than the absorption of the drug. **Bioavailability** is a term used to indicate the proportion of a drug dose that reaches its intended site of action when administered by any route.

Distribution

Following a drug's administration and subsequent absorption into the systemic circulation, the drug becomes distributed into interstitial and intracellular fluids by passive mechanisms such as diffusion or by specific drug transport mechanisms. Distribution of the drug varies depending on multiple factors, including the size of the drug molecule, the drug's affinity for aqueous and lipid tissues, tissue permeability, systemic circulation, protein binding, and pH. These factors collectively determine the rate of delivery and potential amount of drug distributed into tissues.

There are two main phases of distribution. The first phase occurs when most of the well-perfused organs (e.g., liver, kidney, and brain) receive most of the drug. During the second phase of distribution, the less well-perfused organs receive concentrations of the drug. These less well-perfused organs include muscle, most viscera, skin, and fat. This second distribution phase may require minutes to several hours before the concentration of the drug in tissue is in equilibrium with the concentration in the circulation. Several clinically important pharmacokinetic processes occur as a drug is distributed.

Steady State

Steady state refers to the concentration of a drug in the systemic circulation that will eventually be achieved

© Jones & Bartlett Learning, LLC. NOT FOR SALE OR DISTRIBUTION.

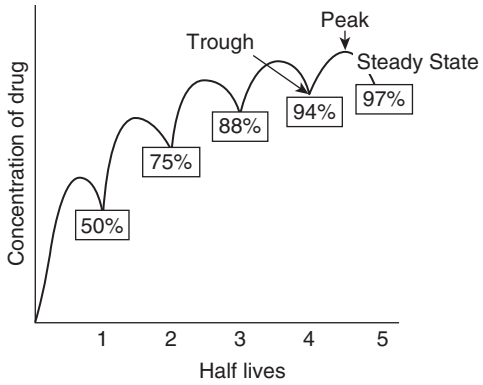


Figure 2-5 Steady state after repeated drug dosing.

when the rate of drug elimination equals the rate of drug availability.[7] This concept is often used in calculations of drug dose and interval between doses (Figure 2-5).

Half-Life

Half-life refers to the time it takes for the plasma concentration or the amount of drug in the body to be reduced by 50% or one half. Half-life is important because it determines the time required to reach steady state and the dosage interval. Steady state is usually reached after 4 to 5 half-lives. Complete **elimination** also takes approximately 4 to 5 half lives once the drug is no longer administered; (Figure 2-6).

Another important concept when considering drug administration is loading dose. A **loading dose** is one or a series of doses that may be given at the onset of therapy with the aim of achieving the target plasma concentration rapidly. This dose, or series of doses, is used to rapidly attain a steady state when the treatment of the individual necessitates a quick therapeutic response.

Volume of distribution refers to the apparent volume (V_D) in which the drug is dissolved. In other words, V_D relates to the concentration of drug in plasma and the amount of drug in the body. The volume of distribution does not have a true physiologic meaning in terms of an anatomic space. However, it often is used to calculate the loading dose of a drug that will immediately achieve a desired steady-state drug level because it refers to the relationship between the dose of the drug administered and the serum concentration after administration.

Plasma Protein Binding

Protein binding is perhaps the most important factor when a drug is in the systemic circulation. Plasma protein

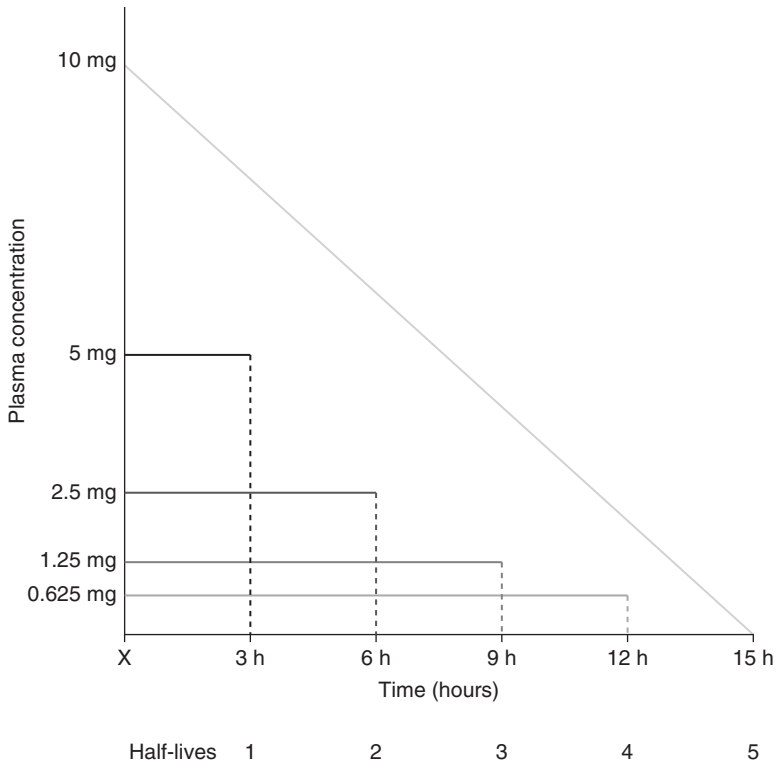


Figure 2-6 Elimination half-life determination.

© Jones & Bartlett Learning, LLC. NOT FOR SALE OR DISTRIBUTION.

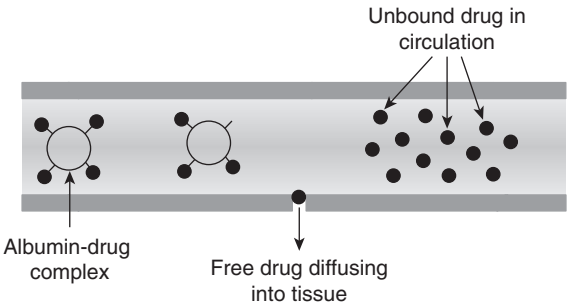


Figure 2-7 Protein binding of drugs.

binding refers to the fraction of total drug in the plasma that is bound to plasma proteins. Many drugs bind to proteins in plasma (Figure 2-7). More than 60 plasma proteins can bind to drugs, but albumin is the most common protein that does so. Albumin is a major carrier for acidic drugs, whereas the protein α_1-acid glycoprotein binds drugs that are basic in nature.

The amount of drug that is bound to plasma proteins is determined by the drug concentration in the systemic circulation, the affinity of the binding sites on the protein for the drug, and the number of binding sites. This concept is important because only the unbound (free) drug can distribute to its intended site of action in tissue; a drug's physiologic effect is related to the free concentration rather than the total circulating plasma drug concentration. The binding of drug to protein is readily reversible, lasting only a half of a millisecond, and the drug continually shifts from bound to unbound status.[6] Binding sites are limited, however, so they may eventually become saturated. When this phenomenon occurs, the risk for drug toxicity increases. For drugs that are normally highly protein bound, even small changes in the extent of binding can produce a large change in the amount of unbound drug and, in turn, a large change in drug effect. Factors that can increase or decrease the amount of protein available for protein-binding include myocardial infarction, surgery, neoplastic disease, rheumatoid arthritis, renal disorders, liver compromise, and burns.

In contrast to drugs that adhere to the protein-binding concept, many drugs accumulate in tissues at higher concentrations than in the extracellular fluids and blood. This pattern may be a result of active transport into the tissue, but more commonly it is a result of tissue binding. Tissue binding is often reversible. When a large fraction of drug is tissue bound, it may serve as a reservoir that prolongs drug action in that same tissue or at a distant site reached through the circulation. Caution must be exercised when prescribing drugs that are highly tissue bound. For example, the aminoglycoside antibiotic known as gentamicin (Garamycin) has a high affinity for kidney tissue, and it can cause local toxicity to the kidney if drug levels become too high.

Other examples of tissue binding include drugs that are lipophilic, which have a high affinity for fat and for bone.[8] Highly lipid-soluble drugs can be stored in fat tissues, which results in fat becoming a drug reservoir. Fat is a relatively stable reservoir because it has low blood flow. Bone is another tissue that is subject to tissue binding of lipophilic drugs. Such drugs can accumulate in bone by adsorption onto the bone crystal surface with eventual incorporation into the crystal lattice.

The Blood–Brain Barrier

The distribution of drugs into the central nervous system (CNS) from the blood is unique. The endothelial cells in the capillaries surrounding the brain are packed very tightly together, which disallows passive transport of materials in the blood out into the surrounding cerebral tissue. This **blood–brain barrier** creates a natural barrier to the exchange of drugs between the blood and the brain.[8,9] A drug must be able to travel *through* the endothelial cells to penetrate this barrier. In the rest of the body, the drug is often able to pass between endothelial cells because the cells are not joined as tightly. For a drug to be able to pass into the brain, it must be highly lipophilic; the more lipophilic a drug is, the more likely it is to pass through the blood–brain barrier.

Another natural drug barrier is the placenta. Fundamentally, the placenta is the organ of exchange between the mother and fetus. The placenta was once viewed as an absolute barrier to drugs and an agent of protection for the fetus, but today it is well known that this belief is flawed. The fetus is exposed to some extent to all drugs taken by the mother. Lipid solubility, the extent of plasma binding, and the degree of ionization of weak acids and bases are important general determinants of drug transfer across the placenta. Additionally, transmembrane proteins that function as efflux transporters are present in the placenta. The export transporters move drugs that diffuse into the placental cell back out into the maternal circulation and thereby limit fetal exposure to potentially toxic agents. Additional information about the use of drugs in pregnancy can be found in the *Pregnancy* chapter.

Drug Transporters: P-Glycoproteins

Some cells have transmembrane proteins that transport drugs and other chemicals out of the cell and into the

© Jones & Bartlett Learning, LLC. NOT FOR SALE OR DISTRIBUTION.

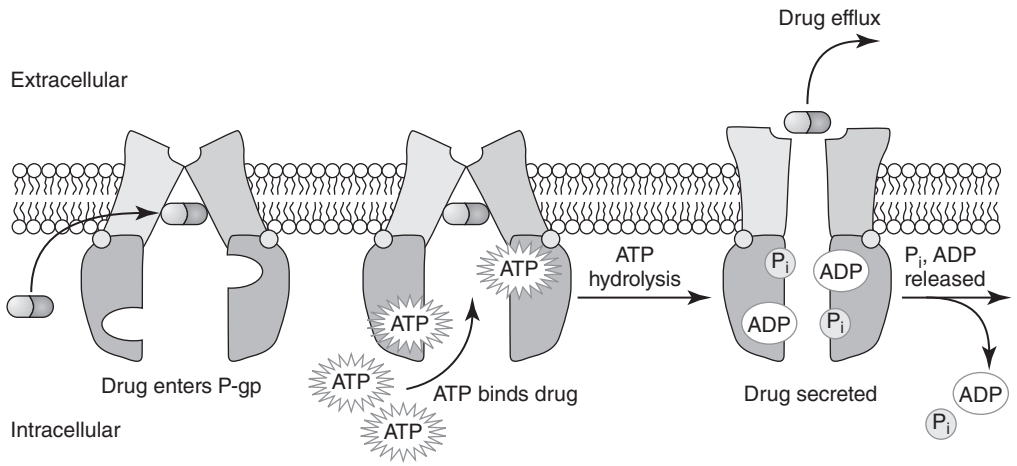


Figure 2-8 Drug transporters: P-glycoprotein in intestinal epithelial cell membranes.

circulation. One such drug transporter is permeability glycoprotein (P-gp), which is also known as multidrug resistance protein 1 (MDR1) or ATP-binding cassette subfamily B member 1 (ABCB1). P-gp, which is encoded by the *ABCB1* gene, functions as an efflux transporter. Fueled by ATP, this transmembrane protein transports drugs and other **xenobiotics** out of cells into the extracellular fluid (Figure 2-8).[10] P-gp is found in the plasma membranes of organs that affect drug absorption (epithelial cells in the intestinal tract), drug distribution (CNS, blood–brain barrier, and placenta), drug metabolism (liver), and drug elimination (kidney). The primary function of P-gp appears to be transporting harmful substances out of body tissues and preventing harmful agents from crossing the blood–brain barrier. P-gp substrates are generally large lipophilic compounds. Some drugs can inhibit or encourage expression of P-gp, thereby affecting the plasma concentration of the P-gp substrate.

Although the clinical implications and role of P-gp and other drug transporters have not been fully elucidated, it is clear they play important roles in drug response. Because these proteins are polymorphic, their role is reviewed further in the *Pharmacogenetics and Pharmacogenomics* chapter.

Metabolism

Termination of a drug's effects by the body is achieved via metabolism and elimination. Drug metabolism refers to the process by which a drug is chemically converted in the body to a metabolite. This transformation is usually enzymatic, and the enzymes responsible are mainly located in the liver. Other tissues, such as kidney, lung, small intestine, and skin, also contain enzymes that metabolize drugs. These reactions are classified as either **phase I reactions** or **phase II conjugation reactions**.[11]

The two-step process of phase I and phase II reactions make the drug molecule hydrophilic so the drug can be excreted via the kidney. Phase I reactions include oxidation, hydrolysis, and reduction reactions, which generally result in the loss of pharmacologic activity. Phase II conjugation reactions involve conjugation to form glucuronides, acetates, or sulfates. Both types of reactions play a major role in diminishing the biologic activity of a drug.

For most drugs, metabolism results in a pharmacologically inactive compound; however, a few drugs are transformed in the body to metabolites that have pharmacologic activity. These drugs are referred to as **prodrugs**. For example, valacyclovir (Valtrex) is not an effective antiviral drug, but its active metabolite, acyclovir, is active against herpes viruses.[12] Prodrugs are being developed intentionally to improve drug stability, increase systemic drug absorption, or prolong the duration of drug activity. When drugs are metabolized into inactive metabolites that are excreted, all is well. However, drug metabolism may also result in adverse health consequences. Therefore, a review of these mechanisms is in order.

The Cytochrome P-450 Enzymes

The **cytochrome P-450 (CYP450)** enzyme family is responsible for the majority of drug metabolism reactions.[13] The name P-450 was chosen because these enzymes are bound to membranes within mitochondria or endoplasmic reticulum within the cell (cyto) and because they contain a heme pigment that absorbs light at a wavelength of 450 nm when exposed to carbon monoxide. Each enzyme name

© Jones & Bartlett Learning, LLC. NOT FOR SALE OR DISTRIBUTION.

Table 2-2 Naming Convention for Cytochrome P-450 Enzymes

Nomenclature	Definition
CYP	Cytochrome P-450 enzyme
CYP1	Family designation
CYP1A	Subfamily A
CYPY1A1	Individual enzyme within subfamily
CYP1A1*1A	Allelic variant of the individual enzyme

reflects a family, subfamily, and then an individual number (Table 2-2). For example, CYP2D6 is number 6 in the subfamily "D" in the "2" family.[13] Currently, 57 different CYP450 enzyme genes have been identified, but only a few of these enzymes are responsible for the majority of drug metabolism in humans.[14] Three types of CYP450 isoforms (CYP1, CYP2, and CYP3) predominate in the metabolism of most commonly used pharmaceuticals.

The various ways these enzymes act represents perhaps the most interesting and most important set of processes that providers must know to prescribe drugs safely. Each CYP450 enzyme is encoded by a specific gene, and each human has two genes that determine expression of enzymatic activity—one inherited from the individual's mother and the other inherited from the individual's father. When a gene mutation occurs that results in an alternate version of the gene, the genes are referred to as **alleles**. Several alleles or variants of one gene may exist. When more than 1% of the population has naturally occurring variant alleles, the variations are collectively referred to as **polymorphism**. Some polymorphisms produce functional changes in the protein product of that gene. The genes that encode CYP450 enzyme activity, for example, are polymorphic. Thus, the clinical expression and functional ability of CYP450 enzymes to metabolize specific drugs ranges from absent to highly efficient depending on which alleles of the specific CYP450 gene an individual has inherited.[15]

The allele type is noted in the name following an asterisk. Thus, for example, CYP2C19*3 is a third allele variant of CYP2C19.

In addition, there are genetic, racial, and sex differences in CYP450 activity. These variations are reviewed in more detail in the *Pharmacogenetics and Pharmacogenomics* chapter.

Drug Interactions

Drugs can interact with many other substances, such as other drugs, herbs, and nutrients. These interactions can have important pharmacotherapeutic consequences.

Drug–Drug Interactions

The function of CYP450 enzymes, can be significantly affected by the presence of drugs, food, herbs, and even vitamin supplements (Table 2-3). **Drug–drug interactions** refer to a modification of an expected drug response due to an exposure to another drug or substance at approximately the same time. Most commonly, drug–drug interactions occur when two drugs are coadministered and are metabolized by the same CYP450 enzyme.

Drugs are typically classified as **inhibitors** or **inducers** of CYP450 enzymatic activity. For example, Drug A might inhibit the activity of CYP3A4 and normally metabolizes Drug B. This results in an increase in the serum concentration of Drug B and subsequent risk of toxicity by Drug B. Conversely, administration of Drug A may induce more CYP3A4 activity and increase the metabolism of Drug B, thereby decreasing the serum concentration and the pharmacologic activity of Drug B. The effect of inducers occurs more slowly than the effect of inhibitors because it takes a while to produce more of the relevant CYP enzymes. Since most of these drug–drug interactions are due to CYP450 enzymes, it is important to determine the identity of the CYP450 enzyme that metabolizes a particular drug, to research the effects of the drug–drug interaction, and to educate individuals when coadministering drugs that are metabolized by the same enzyme.[12]

Coadministering drugs with known drug–drug interactions is sometimes done intentionally. An example of intentional coadministration can be found in the treatment of persons who are infected with the human immunodeficiency virus (HIV). Ritonavir (Norvir), a strong inhibitor of CYP3A4 and CYP2D6, is commonly coadministered with atazanavir (Reyataz), thereby increasing plasma levels and the anti-HIV activity of atazanavir. The ritonavir acts to boost the atazanavir concentration in the body.

Two different drugs can also be put together in one combination formulation to minimize drug interactions and facilitate patient adherence. Individuals with HIV and acquired immunodeficiency syndrome (AIDS) were prescribed a medication regimen that required taking 30 medications daily prior to the development of highly active antiretroviral therapy combination drugs; the combination drugs now allow them to take significantly fewer pills.

Drug–drug interactions can also occur when two drugs are given concomitantly and interact via their pharmacokinetic or pharmacodynamic processes. For example, additive effects of drugs that cause CNS sedation can, at the extreme, cause unconsciousness. When phenytoin (Dilantin) is given with salicylates (e.g., aspirin), the plasma

© Jones & Bartlett Learning, LLC. NOT FOR SALE OR DISTRIBUTION.

Table 2-3 Examples of CYP450 Enzymes That Frequently Metabolize Drugs and Their Pharmacologic Effects[a]

Inhibitors[b]: Generic (Brand)	Inducers[c]: Generic (Brand)	Substrates[d]: Generic (Brand)
CYP1A2		
Fluoroquinolones: ciprofloxacin (Cipro), clarithromycin (Biaxin) Combination oral contraceptives Other: amiodarone (Cordarone), cimetidine (Tagamet), erythromycin (E-Mycin), fluvoxamine (Luvox), isoniazid (INH)	Carbamazepine (Tegretol), insulin, phenobarbital (Luminal), phenytoin (Dilantin), primidone (Mysoline), rifampin (Rifadin), tobacco	Antidepressants: amitriptyline (Elavil), clomipramine (Anafranil), clozapine (Clozaril), desipramine (Norpramin), fluvoxamine (Luvox), imipramine (Tofranil) Antipsychotics: haloperidol (Haldol) Other: acetaminophen (Tylenol), caffeine, theophylline (Theo-Dur)
CYP2C9		
Anti-infectives: fluconazole (Diflucan), isoniazid (INH), metronidazole (Flagyl), ritonavir (Norvir), trimethoprim/sulfamethoxazole (Septra) Other: amiodarone (Cordarone), cimetidine (Tagamet), fluoxetine (Prozac), fluvoxamine (Luvox)	Carbamazepine (Tegretol), phenobarbital (Luminal), phenytoin (Dilantin), primidone (Mysoline), rifampin (Rifadin)	Carvedilol (Coreg), celecoxib (Celebrex), diazepam (Valium), glipizide (Glucotrol), glyburide (Micronase), ibuprofen (Advil, Motrin), irbesartan (Avapro), losartan (Cozaar)
CYP2C19		
Fluoxetine (Prozac), fluvoxamine (Luvox), isoniazid (INH), modafinil (Provigil) , omeprazole (Prilosec), ritonavir (Norvir), topiramate (Topamax)	Carbamazepine (Tegretol), phenobarbital (Luminal), phenytoin (Dilantin), rifampin (Rifadin)	Omeprazole (Prilosec), phenobarbital (Luminal), phenytoin (Dilantin)
CYP2D6		
Amiodarone (Cordarone), cimetidine (Tagamet), diphenhydramine (Benadryl), fluoxetine (Prozac), paroxetine (Paxil), quinidine, ritonavir (Norvir), sertraline (Zoloft)	No significant inducers	Antidepressants: amitriptyline (Elavil), clomipramine (Anafranil), desipramine (Norpramin), doxepin (Sinequan), fluoxetine (Prozac), imipramine (Tofranil), paroxetine (Paxil), venlafaxine (Effexor) Antipsychotics: haloperidol (Haldol), risperidone (Risperdal), thioridazine (Mellaril) Beta blockers: carvedilol (Coreg), metoprolol (Lopressor), propranolol (Inderal) Opiates: codeine, tramadol (Ultram) Other: donepezil (Aricept), ondansetron (Zofran)
CYP3A4		
Azole fungals: fluconazole (Diflucan), itraconazole (Sporanox), ketoconazole (Nizoral) Anti-infectives: clarithromycin (Biaxin), ciprofloxacin (Cipro), erythromycin (E-Mycin), isoniazid (INH), metronidazole (Flagyl), ritonavir (Norvir) Other: amiodarone (Cordarone), cimetidine (Tagamet), diltiazem (Cardizem), verapamil (Calan)	Carbamazepine (Tegretol), St. John's wort, dexamethasone, phenobarbital (Luminal), phenytoin (Dilantin), protease inhibitors, rifampin (Rifadin)	Alprazolam (Xanax), amlodipine (Norvasc), atorvastatin (Lipitor), cyclosporine (Sandimmune), diazepam (Valium), estradiol (Estrace), simvastatin (Zocor), sildenafil (Viagra), verapamil (Calan), zolpidem (Ambien)

[a] This table is not comprehensive as new information is being generated on a regular basis.
[b] These drugs inhibit the metabolism of substrates by these CYP450 enzymes.
[c] These drugs induce production of the CYP450 enzyme, which causes increased metabolism of the substrate.
[d] The plasma levels of these drugs are increased by inhibitors and decreased by inducers of the specific CYP450 enzyme responsible for their metabolism.
Source: Data from Lynch T, Pice M. The effect of cytochrome P450 metabolism on drug response, interactions, and adverse effects. *Am Fam Phys.* 2007;76:391-396.[15]

© Jones & Bartlett Learning, LLC. NOT FOR SALE OR DISTRIBUTION.

levels of free phenytoin increase because the salicylates compete for plasma protein binding. Phenytoin has a very **narrow therapeutic index** and increased levels can reach toxic levels quickly, resulting in ataxia, nystagmus, or increased seizure activity.

P-Glycoprotein Drug Interactions

P-glycoprotein activity can also be increased or decreased by a number of endogenous and environmental stimuli. In a similar fashion to the CYP450 system, some drugs act as substrates (inducers) and others as inhibitors of P-glycoprotein expression. P-glycoprotein inhibition can result in increased plasma levels of a specific drug; conversely, P-glycoprotein induction can result in more rapid metabolism or elimination and decreased plasma levels of the drug in question. St. John's wort is a potent inducer of P-glycoprotein; when this herb is given concomitantly with digoxin (Lanoxin), the plasma levels of digoxin decrease because the augmented intestinal P-glycoprotein activity effectively keeps digoxin out of the systemic circulation.

Drug–Nutrient Interactions

Drug metabolism can also be influenced by diet. Previously these interactions were termed drug–food interactions, but they are more appropriately termed **drug–nutrient interactions**. Nutrients can affect drug bioavailability via two mechanisms: (1) decreased or delayed oral bioavailability via interference with absorption and (2) increased bioavailability via inhibition of CYP3A in the cells of the intestinal wall.[16] This second mechanism increases plasma levels of the drug metabolized by CYP3A and can precipitate adverse drug reactions or toxicities.[17]

Components in grapefruits and grapefruit juices (naringin and furanocoumarins) are potent inhibitors of CYP3A (Box 2-1).[16,18,19] Persons who take a medication that has a narrow therapeutic index and is metabolized by CYP3A are more likely to have an adverse drug reaction if the medication is taken within 48 hours of ingesting grapefruit juice. Table 2-4 provides a list of drugs that have a clinically significant interaction with grapefruit juice.

Another clinically important drug–nutrient interaction is the hypertensive crisis that can occur among persons taking monamine oxidase (MAO) inhibitors while eating a diet of protein-rich foods that are high in tyramine (often foods that are aged, fermented, pickled, or smoked). Table 2-5 lists additional important drug–nutrient interactions.[20,21]

Table 2-4 Examples of Grapefruit Juice–Drug Interactions

Drug: Generic (Brand)	Clinical Effect of Increased Serum Concentration of Drug When Taken with Grapefruit Juice
Antiarrhythmics	
Amiodarone (Cordarone)	Thyroid, pulmonary, or liver injury; cardiac arrhythmias, prolonged QT syndrome, bradycardia
Quinidine	Torsades de pointes
Benzodiazepines	
Diazepam (Valium)	Increased CNS depression
Midazolam (Versed)	Increased CNS depression
Triazolam (Halcion)	Increased CNS depression
Calcium-Channel Blockers	
Felodipine (Plendil)	Flushing, peripheral edema, headaches, hypotension, tachycardia
Nicardipine (Cardene)	Flushing, peripheral edema, headaches, hypotension, tachycardia
Nimodipine (Nimotop)	Flushing, peripheral edema, headaches, hypotension, tachycardia
Verapamil (Covera-HS)	Flushing, peripheral edema, headaches, hypotension, tachycardia
CNS Depressants	
Buspirone (BuSpar)	Increased adverse effects of buspirone
Carbamazepine (Tegretol)	Increased adverse effects of carbamazepine
Clomipramine (Anafranil)	Increased effect of clomipramine
Sertraline (Zoloft)	Increased adverse effects of sertraline
Statins	
Atorvastatin (Lipitor)	Increased levels of atorvastatin can cause rhabdomyolysis
Lovastatin (Mevacor)	Increased levels of lovastatin can cause rhabdomyolysis
Pravastatin (Pravachol)	Increased levels of pravastatin can cause rhabdomyolysis
Simvastatin (Zocor)	Increased levels of simvastatin can cause rhabdomyolysis

Abbreviation: CNS = central nervous system.

Drug–Herb Interactions

Drug–herb interactions are particularly difficult to assess.[22] Most herbal products obtained over the counter are considered dietary supplements and, therefore, are not regulated as drugs.[23-25] Thus, there is wide variation in the pharmaceutically active compounds in different herbal preparations, and some may include components that are harmful. Nonetheless, adverse effects are known to occur when specific herbs and drugs are taken concomitantly with regulated medications. Individuals taking warfarin (Coumadin) can have increased bleeding if they take *Salvia miltiorrhiza* (Danshen) or garlic preparations.

Some of the most well-known herb–drug interactions are associated with use of St. John's wort.[27] This herb has

© Jones & Bartlett Learning, LLC. NOT FOR SALE OR DISTRIBUTION.

Table 2-5 Examples of Clinically Important Drug–Nutrient Interactions[a]

Drug: Generic (Brand)	Foods	Mechanism of Action	Clinical Implications
Angiotensin-converting enzyme (ACE) inhibitors	High-potassium foods such as bananas, oranges, legumes, meats, salt substitutes	ACE inhibitors spare potassium so the addition of food high in potassium can cause toxicity.	Bradycardia and potential cardiac arrest
Digoxin	High-fiber products such as bran, pectin, bulk laxatives	Decreases absorption of digoxin.	Insufficient digoxin effect
MAO inhibitors	Absolute: aged cheese, aged and cured meat, sausage, banana peel, fava bean pods, Marmite or yeast extracts, sauerkraut, soy sauce, tap beer Moderate: red and white wine, bottled or canned beer	Monoamine oxidase found in the GI tract inactivates tyramine. Tyramine can cause hypertension when absorbed into the systemic system.	Severe hypertensive reaction
Quinolones, antifungals, and tetracyclines	Dairy products, calcium supplements, calcium-fortified orange juice, antacids, iron-containing vitamins	Drugs bind to iron and calcium in the GI tract and form a compound that is excreted without entering the systemic system.	Decreased absorption of the antibiotic
Theophylline (Theo-Dur)	High-fat meal	High-fat meals increase absorption of theophylline.	Theophylline toxicity: nausea, vomiting, headache, irritability
Warfarin (Coumadin)[b]	Alcohol		More than three drinks/day increases effect of warfarin
	Foods with vitamin K must be used with consistency: broccoli, Brussels sprouts, turnip greens, kale, spinach	Large amounts of vitamin K interfere with the effect of warfarin.	Inadequate anticoagulation

[a] This table is not comprehensive as new information is being generated on a regular basis.
[b] Warfarin has multiple drug–drug, drug–nutrient, and drug–herb interactions.
Sources: Data from Chen J, Wilkinson J. The monoamine oxidase type B inhibitor rasagiline in the treatment of Parkinson disease: is tyramine a challenge? *J Clin Pharmacol.* 2012;52:620-628[19]; Gardner DM, Shulman KI, Walker SE, Tailor SA. The making of a user friendly MAOI diet. *J Clin Psychiatry.* 1996;57:99-104.[25]

Box 2-1 The Grapefruit Juice Story

In 1989, a group of researchers used grapefruit juice to mask the taste of alcohol in a study that was evaluating possible interactions between alcohol and felodipine (Plendil), a calcium-channel blocker used to treat hypertension. Thestudy participants developed increases in plasma felodipine levels that were unrelated to alcohol or known felodipine pharmacokinetics. The culprit was the grapefruit juice!

Grapefruit has a number of constituents that inhibit the function of CYP3A4 enzymes in the cells of the intestinal lumen. Because CYP3A4 metabolizes many drugs before they enter the systemic system, inhibition of CYP3A4 can cause increased plasma levels of drugs, adverse drug reactions, and/or toxicity.

How much grapefruit juice does it take? Is it just the juice or does a grapefruit eaten for breakfast have the same effect? What about different types of grapefruit? Here is the story:

Grapefruit juice irreversibly inhibits CYP3A4, so new enzymes must be synthesized before normal function is restored. Thus, 30% of the inhibitory effect is still present 24 hours after ingestion of a single 8-oz glass of normal strength grapefruit juice. It is recommended that medications affected by grapefruit juice not be taken until 72 hours after the last glass of grapefruit juice. Unfortunately for grapefruit juice lovers, the effect is the same if they drink white, pink, or ruby red juice.

© Jones & Bartlett Learning, LLC. NOT FOR SALE OR DISTRIBUTION.

purported effectiveness for the treatment of individuals with depression. However, placebo trials of St. John's wort have been inconclusive and meta-analyses have concluded that it might be effective for mild depression only.[28] In addition, St. John's wort is an enzyme inducer and decreases the plasma levels of many drugs, including midazolam (Versed), digoxin (Lanoxin), warfarin (Coumadin), and oral oxycodone.[29,30] Women who are taking oral contraceptives can also experience breakthrough bleeding when St. John's wort is taken concomitantly with oral contraceptives, and this drug combination may interfere with the contraceptive effectiveness.[29]

Drug-Induced Toxicity

Finally, some metabolites of drugs and herbal dietary supplements are toxic to the liver or to the kidney.[31] In some instances, tests for liver function are required either before therapy with a specific drug is started or during therapy as a way to monitor liver function. The direct toxic effects of drugs or their metabolites on liver and/or kidney function are discussed in more detail in the *Drug Toxicity* chapter.

Excretion

Drug excretion refers to the elimination of a drug molecule or its metabolite from the biologic system. Drugs are primarily excreted via the kidneys, although some excretion does occur via saliva, feces, sweat, and mammary glands. Excretion of drugs in breast milk is important not because of the amounts eliminated, but because the excreted drugs are potential sources of unwanted pharmacologic effects in the nursing infant.

Excretion of drugs and metabolites into urine involves three distinct processes: glomerular filtration, passive tubular reabsorption, and active tubular secretion. All drugs that have a low molecular weight and are not bound to protein are filtered in the glomerulus into the glomerular filtrate. Lipid-soluble drugs move back into the blood via passive tubular reabsorption, but ionized hydrophilic drugs remain in the urine. Some drugs are actively secreted from the circulatory system into the proximal tubule. Penicillin-G is a good example of a drug that is eliminated via tubular secretion. Probenecid (Benemid), which is sometimes administered with Penicillin-G, blocks this mechanism and increases plasma levels of penicillin. Finally, the pH of the urine affects elimination.

Weak acids are excreted more easily in alkaline urine and more slowly when the urine is more acidic; the converse is true for drugs that are weak bases. Alterations in renal function will affect drug dose levels. When deciding on initial doses for drugs that are eliminated renally, the individual's renal function should be assessed. For example, gentamicin (Garamycin) is excreted via the kidney, and it can be toxic to proximal tubule cells. Therefore, when gentamicin is given in large doses or for a prolonged period of time, kidney failure can occur. As the kidney fails, less gentamicin is excreted, which predisposes the individual to additional kidney damage.

Clearance

Clearance is the measure of the body's ability to eliminate a drug.[32] This measure is often used in pharmacokinetic calculations, and it does not identify the mechanism or process of elimination (e.g., the clearance calculation does not consider whether the drug is eliminated by metabolic processes or excretion). This measure is the most important pharmacokinetic parameter because it determines the steady-state concentration for a given dosage route. The mechanisms of drug elimination are complex, but collectively, drug elimination from the body may be quantified using the concept of drug clearance.

Pharmacodynamics

Dose–Response Relationship

Pharmacodynamics is the study of the relationship between the concentration of a drug in the systemic circulation and the biologic response that occurs, often termed the **dose–response relationship**. A **dose–response curve** can be drawn by plotting the concentration of the drug on the *x*-axis and the response on the *y*-axis (Figure 2-9). The **minimum effective concentration** is the lowest dose at which a desired response is noted. A corollary concept, applied to the effect of antimicrobials, is minimum inhibitory concentration, meaning the lowest dose at which the antimicrobial inhibits visible growth of a microorganism overnight. The same dose of a drug often results in different plasma concentrations among individuals. This difference is secondary to individual differences in pharmacokinetic parameters. For example, the onset, intensity, and duration of response an individual experiences depend on both the dose of the drug administered and the pharmacokinetics of the drug in that individual.

Two important parameters can be calculated in drawing dose–response relationship curves for particular drugs. **Potency** is the concentration at which the drug elicits 50%

© Jones & Bartlett Learning, LLC. NOT FOR SALE OR DISTRIBUTION.

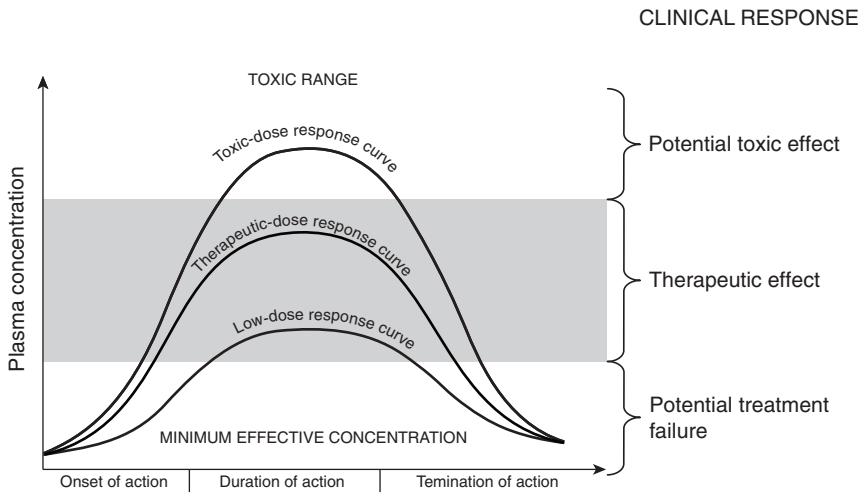


Figure 2-9 Dose–response curve.

of its maximal response. **Efficacy** is the maximal response produced by the drug. A clinical example of a study of pharmacodynamics is recording changes in blood pressure when a woman is being treated with antihypertensive medications. According to this concept, there is a drug receptor located within the target organ tissue. When a drug molecule finds and attaches to the receptor target, it forms a complex with that target that causes the biologic response, which is the specific mechanism of action of that drug.

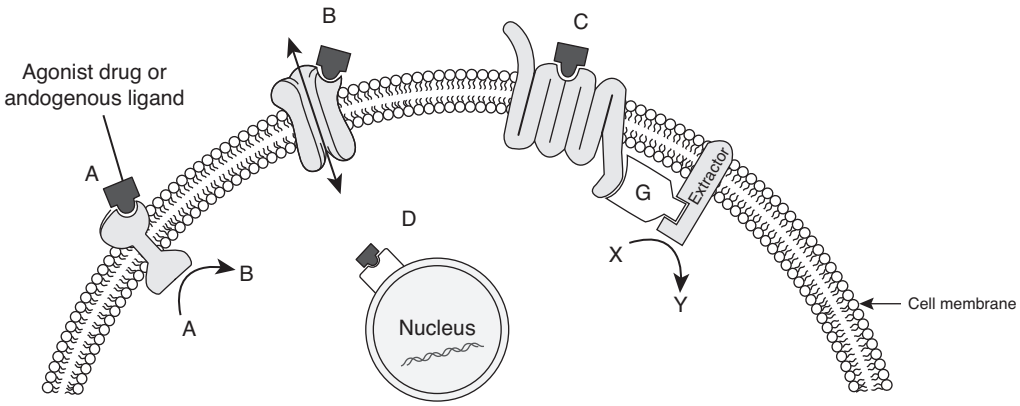
Drug–Receptor Interactions: The Role of Cell Membrane Receptors

For a clinician to make rational therapeutic decisions, the prescriber must understand how drug–receptor interactions underlie the relationship between dose and response. A receptor is the cell component that interacts with a drug to produce a psychophysiologic effect. Drug receptors are often proteins, and common examples include receptors for hormones, growth factors, transcription factors, and neurotransmitters; the enzymes that play a role in crucial metabolic or regulatory pathways; proteins involved in transport; secreted glycoproteins; and structural proteins. Receptors are the governing agent in determining the dose for any drug. Specifically, the **affinity**, or propensity of a drug to bind with a specific receptor, determines the drug concentration necessary to achieve the desired effect. Drugs have a specific affinity for a particular cellular receptor. Drug binding to the receptor will either increase or decrease the rate of the biologic response controlled by that specific receptor. Note that drug–receptor binding does not change the physiologic activity, but simply either enhances or blocks it.

Four receptor systems are commonly cited: (1) embedded enzymes; (2) ligand-binding ion channels; (3) G-protein–coupled receptors; and (4) the nuclear receptors that are on the nuclear or mitochondrial membrane called transcription factors (Figure 2-10). The receptor of a cell membrane–embedded enzyme extends across the cell membrane, with the ligand-binding area located on the cell surface and the site for the enzyme activity located on the intracellular portion of the receptor. The response time of these receptors is usually within seconds. Insulin and atrial natriuretic factor are endogenous **ligands** that affect target cells via this signaling mechanism. Ligand-binding ion channels are similar to the embedded enzymes, in that the ion channels cross the cell membrane. These receptors control the flow of ions into and out of the cell. The ligand-binding domain is specific for a precise ion (e.g., calcium). With binding of the ligand to the receptor, the channel opens, allowing ions to flow into or out of the cell. Responses in this system commonly occur in milliseconds. The neurotransmitter acetylcholine and the amino acid glycine act through this receptor family.[33]

The **G-protein–coupled receptor** family is the largest group of cell-surface receptors, and approximately 30% of the drugs used today interact with these receptors (Box 2-2). Therefore, these receptors are of particular importance in pharmacology.[34] The G-protein–coupled receptor has three parts: the receptor, the G-protein, and the effector or second messenger. These receptors may be located on the cell surface or in a pocket accessible from the cell surface. Ligands bind to the receptors on the exterior portion of the cell membrane. Intracellularly, the bound receptors act as a catalytic enzyme. The second messenger then interacts

© Jones & Bartlett Learning, LLC. NOT FOR SALE OR DISTRIBUTION.



(A) Embedded enzyme: When a drug binds to the extracellular domain of this receptor, an enzymatic intracellular domain function is activated or inhibited. (B) Ligand-binding ion channel: The drug binds to the extracellular portion of this transmembrane protein complex, which causes it to change shape and alter conductance. (C) G-protein–coupled receptors are also known as seven transmembrane domain receptors. When a drug binds to the extracellular domain of this receptor, a G-protein in the intracellular space is activated to stimulate an effector mechanism. (D) Transcription factor: A lipid-soluble drug crosses the cell membrane and binds to an intracellular or nuclear receptor.

Figure 2-10 Four receptor types.

with intracellular components. The G-protein stimulates the enzyme adenyl cyclase to change ATP to cyclic AMP (cAMP) intracellularly, with subsequent activation of protein kinases and cellular reactions. Drugs acting via a G-protein–coupled receptor include beta blockers and antiasthma drugs.[35]

In contrast, transcription factors are intracellular receptors that have a longer response time. Lipid-soluble ligands cross the cell membrane to reach these receptors, which are located in the cell nucleus on DNA, where the transcription factors regulate protein synthesis. Activation of these receptors stimulate the transcription of messenger RNA templates for protein synthesis. With transcription factors there is a response time ranging from hours to days. Steroid hormones, such as estrogen and progesterone, act through these intracellular receptor sites.[36]

Agonists, Partial Agonists, and Antagonists

Agonists are drugs that elicit a pharmacologic response when interacting with the receptor. Such agents shift the equilibrium between the active and inactive forms

Box 2-2 Gone But Not Forgotten: Alfred Gilman

In 1941, two births occurred with significance for pharmacology—a book and a boy. In that year, two young researchers at Yale University, physician Louis Goodman and pharmacologist Alfred Gilman, published the first edition of their book, *The Pharmacological Basis of Therapeutics*. This internationally popular text has endured for more than 7 decades as the "bible" of pharmacology. As of 2011, a dozen editions had been published.

In the same year, Alfred Gilman and his wife had a son. In honor of their friend and the coauthor of the book, they named him Alfred Goodman Gilman. The younger Gilman went on to obtain both a degree as a physician and a PhD in pharmacology. He later was a contributing editor in the aforementioned prestigious text. But his major claim is his discovery regarding G-proteins. Martin Rodbell had found that guanosine-5′ triphosphate (GTP) was integral to actions within a cell. However, it was Alfred G. Gilman who discovered that the G-proteins actually are the molecular switches between activation of receptors on the cell and the actions within the cell. Knowledge of G-proteins and cellular activity is an invaluable asset in understanding drug actions and for drug design. For this work, Rodbell and Alfred G. Gilman shared the 1994 Nobel Prize in Physiology or Medicine.

Thus, two births in 1941 have added immeasurably to knowledge in pharmacology and health care.

© Jones & Bartlett Learning, LLC. NOT FOR SALE OR DISTRIBUTION.

of the receptor in the direction of the active form: By binding the active form more avidly (i.e., they induce a conformational change in the receptor that leads to a maximal effect), they drive the physiologic response in the direction of activation. Insulin and morphine are of examples of drugs that act as receptor agonists. Affinity refers to the degree of attraction between a drug and receptor. Drugs with high affinity bind more extensively to the receptor than a drug with less affinity. A **partial agonist** is a drug that elicits a partial pharmacologic response when bound to a specific receptor. Partial agonists have only a slightly higher affinity for the active receptor than for the inactive form, so they display some agonist activity and they interfere with the function of a full agonist. Buspirone (BuSpar), which is used to treat general anxiety disorder, is a partial agonist. **Agonist–antagonists** are similar to partial agonists in that they have an effect that is not as potent as full agonist stimulation. These drugs affect receptors that have different forms, and they act as an agonist at one form and as an antagonist at another. Butorphanol (Stadol), for example, blocks the effect of morphine at the mu opioid receptor but stimulates the kappa opioid receptor; the net result is analgesia that is not as potent as the effect obtained with morphine.

An **antagonist** is a drug that inhibits the action of an agonist when bound to the receptor and has no effect on the agonist itself. Antagonists may have a high affinity for the receptor, but they do not activate the receptor when bound to it. Although antagonists do not initiate a response, they prevent activation of the receptor by an agonist and, therefore, have a pharmacologic effect. The physiologic response to drugs acting as antagonists depends on the presence of an agonist. For example, antihistamines and naloxone (Narcan) are examples of antagonists.

Antagonists can be competitive or noncompetitive. A **competitive antagonist** occurs when the antagonist has equal affinity for both the active and inactive conformations of the receptor and competes with an agonist for binding to the active form of the receptor. Ligands with the highest affinity will bind with the receptor. If there is an equal affinity, then the ligand in the highest concentration will bind with the receptor. In contrast, **noncompetitive antagonists** bind with a part of the receptor away from the usual site to which an agonist binds. This causes a structural or functional change in the receptor that inactivates it, so agonist binding at the usual site fails to stimulate the expected physiologic response. The response to competitive antagonists is reversible, in that large enough amounts of the agonist may surmount the inhibitory effect, whereas the effect of noncompetitive antagonists is usually irreversible until the drug is inactivated.

The attractive feature of this model is that it explains **inverse agonists** rather well. If there is a basal tendency of the receptor to be in the active (agonist) state, then these active receptors will demonstrate a tonic, basal agonist effect even in the total absence of agonist ligands binding to them. If one adds an inverse agonist with a preference for the inactive receptor, the equilibrium shifts to the left, and the tonic agonist effect is lessened. Diphenhydramine (Benadryl) is an inverse agonist that binds to histamine receptors thereby suppressing the basal agonist activity.

Therapeutic Effect

All pharmacologic responses must have a maximum effect. The **maximum effect**, also referred to as the ceiling effect, is defined as the point at which no further response is achieved regardless of increasing drug concentration. If the clinician increases the dose of a drug but this does not lead to further clinical response, it is likely that the maximum effect has been reached. There is one other possible explanation: Some target organs may be more or less sensitive to the drug being administered. Therefore, it is important to note the drug dose required for the **therapeutic effect**. For some drugs, there is a narrow **therapeutic range** (or **therapeutic window**). The therapeutic range is the plasma concentration of the drug that produces the desired action without toxicity. Hence, a therapeutic range is between a minimal effective drug dose and the toxic concentration. Lithium (Eskalith), a drug frequently prescribed for women with bipolar disorder, has a narrow therapeutic range of 0.6–1.2 mEq/L with toxic concentrations at serum levels higher than 1.5 mEq/L.

Drugs also must be evaluated for the **therapeutic index** (Figure 2-11). The therapeutic index is the ratio of lethal doses in 50% of the population (LD_{50}) over the median minimum effective dose (ED_{50}) in 50% of subjects.[6] Thus, the therapeutic index is a quantitative measure of the safety of a drug. A drug has a narrow therapeutic index if the difference between the minimum effective concentration and the minimum toxic concentration is less than twofold. The FDA has named approximately 25 drugs as having a narrow therapeutic index (Table 2-6). A drug is safer when the value of the therapeutic index is higher. Lower therapeutic index numbers are associated with an increased risk of toxicity.

Identification of the therapeutic index sets the stage for considering **bioequivalence**. Bioequivalence is determined

© Jones & Bartlett Learning, LLC. NOT FOR SALE OR DISTRIBUTION.

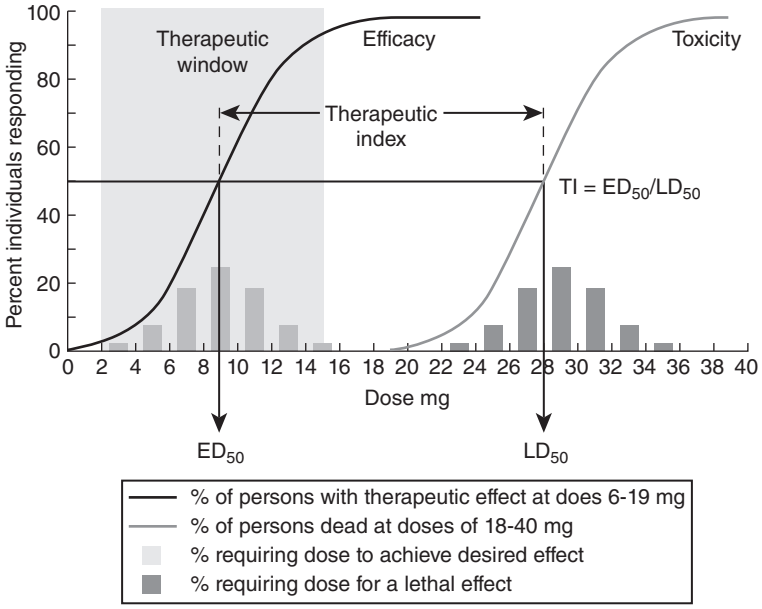


Figure 2-11 Therapeutic index.

by comparing the mean bioavailability of two drug products in multiple samples (individuals). If the mean bioavailability of one drug is within 80% to 125% of another drug, the two are determined to be bioequivalent and can usually be substituted for each other. However, bioequivalence does not guarantee **therapeutic equivalence**, because bioavailability depends on multiple individual factors. For example, an elderly woman with renal compromise may have a pharmacodynamic profile that allows her to metabolize one formulation of digoxin (Lanoxin) to obtain a therapeutic plasma level, but another formulation may result in subtherapeutic plasma levels. If the prescriber does not want the pharmacy to substitute one drug for another that has been determined to be bioequivalent, the words "no substitution" must be written on the prescription.

When drugs with a narrow therapeutic index are being administered intravenously, the trough level should be drawn just before the next dose. In contrast, when gentamicin sulfate (Garamycin) is being administered, blood levels are obtained for **peak levels** 30 minutes after the intravenous infusion ends and trough levels are obtained just before the next dose. The drug dose may be adjusted according to the levels obtained. Peak and trough levels vary with the drug.

Table 2-6 Drugs with a Narrow Therapeutic Index

Drug: Generic (Brand)	Drug: Generic (Brand)
Amphotericin B (Amphotec)	Lithium (Eskalith)
Aminophylline	Metaproterenol sulfate (Alupent)
Carbamazepine (Tegretol)	Minoxidil (Rogaine)
Clindamycin (Cleocin)	Phenytoin sodium (Dilantin)
Clonidine (Catapres)	Prazosin hydrochloride (Minipress)
Digoxin (Lanoxin)	Primidone (Mysoline)
Dimercaprol	Procainamide hydrochloride (Procanbid)
Ethinyl estradiol/progestin oral contraceptives	Quinidine sulfate
Guanethidine sulfate	Theophylline (Theo-Dur)
Gentamicin (Garamycin)	Tricyclic antidepressants
Isoproterenol sulfate (Isuprel)	Warfarin (Coumadin)
Levothyroxine (Synthroid)	Valproic acid (Depakene)

Source: Data from Food and Drug Administration, Center for Drug Evaluation and Research.

Pharmacotherapy

Pharmacotherapeutics refers to the clinician applying knowledge of the benefits and risks of drug therapy to individual care. In addition to pharmacokinetics and pharmacodynamics, other determinants of drug therapy include the age or gender of the person receiving the drugs, past and present health status, family history, lifestyle

© Jones & Bartlett Learning, LLC. NOT FOR SALE OR DISTRIBUTION.

behaviors, and drug compliance. All of these factors must be considered when selecting and monitoring drug therapy. Understanding pharmacokinetics and pharmacodynamics is an important component of pharmacotherapy given the goal of achieving a desired beneficial effect with minimal adverse effects. The pharmacokinetic processes of absorption, distribution, metabolism, and excretion determine how rapidly, in which concentration, and for how long the drug will be present at the target organ. The pharmacodynamic concepts of maximum response, therapeutic index, and drug-receptor interactions determine the magnitude of the effect at a particular concentration. Knowing the relationship between drug concentrations and effects allows the clinician to take into account the various features of an individual that make this person different from the average individual in response to a drug.

Chronobiology/Chronopharmacology

Chronobiology or **chronopharmacology** is the study of pharmacokinetics as related to circadian rhythms or temporal changes. Variations in metabolism may differ by time of day, as well as by the age of the individual. In particular, elderly individuals may evidence changes in metabolism associated with time of day.[37] It has been suggested that use of drugs may be safer as well as more effective if timing of drug administration is considered.[38]

Timing of administration of antihypertensives at bedtime, for example, may result in better blood pressure control.[39] Intriguing chronopharmacology studies have also been conducted regarding the use of aspirin during pregnancy. One randomized controlled trial compared changes in blood pressure in women who took a placebo or low-dose aspirin at one of three times: in the morning, 8 hours after awakening, or at bedtime. Blood pressure was significantly reduced in the women who took aspirin compared to those who took the placebo only when the aspirin was taken 8 hours after awakening and at bedtime. Low-dose aspirin had no effect on blood pressure if taken in the morning.[40] These findings underscore the need for more studies in the area of chronopharmacology.

The Effects of Age

Clearly, a number of factors related to drugs influence drug dose, absorption, and efficacy; however, numerous factors related to the biologic system also influence drug therapy.[37] Newborns and children generally require lower drug doses secondary to their size and their immature hepatic and renal systems. Drugs cannot be metabolized or excreted as effectively due to the immature liver and kidneys, respectively. Likewise, older women may require a decreased dose and are at greater risk for toxicity due to the decreasing efficiency of hepatic metabolism and excretion associated with aging of the hepatic and renal systems. The lowered level of enzyme activity slows the rate of drug metabolism causing higher plasma drug levels per dose compared to young adults. Also, certain diseases that cause impaired renal and liver function mandate dosage adjustments.

Gender Differences in Drug Metabolism

Gender differences in drug metabolism may relate to several factors. Women are generally smaller in stature and weight than men; consequently, when women are prescribed the standard dose for men, they are often found to have higher plasma drug concentrations. In addition, individual differences in water and fat content can affect drug metabolism, as some drugs are more hydrophilic or lipophilic. Women have a slower gastrointestinal transit time during the luteal phase of the menstrual cycle and during pregnancy, which can also affect drug absorption. Women have a 50% to 75% higher risk for having an adverse drug events as men, in large part due to these many gender-related physiologic variations.[36]

Metabolic differences between the sexes have been noted for a number of drugs. This suggests that hormonal activity might affect the activity of certain CYP450 enzymes—a topic discussed in more detail in the *Pharmacogenetics and Pharmacogenomics* chapter. For example, women metabolize diazepam (Valium), prednisolone (Deltasone, Orapred), caffeine, and acetaminophen (Tylenol) slightly faster than their male counterparts. Conversely, men metabolize propranolol (Inderal), chlordiazepoxide (Librium), lidocaine, and some steroids faster than women.

Health Status

Both illness and some normal changes in health status can affect the pharmacokinetics and pharmacodynamics of a given drug. During pregnancy, a woman's reduced gastrointestinal motility and increased gastric pH affect drug absorption. Drug distribution may change because the maternal plasma volume increases by 50% in pregnancy. Serum albumin binding capacity is decreased during pregnancy, which results in an increase in unbound, active drug. Maternal hormones can affect drug metabolism by enhancing or inhibiting metabolism of various drugs.

© Jones & Bartlett Learning, LLC. NOT FOR SALE OR DISTRIBUTION.

Drug excretion may also be affected due to the increase in renal blood flow. Pharmacokinetic and pharmacodynamic changes in pregnancy are discussed further in the *Pregnancy* chapter.

A woman with liver disease and tuberculosis will be unable to take some antitubercular drugs due to their hepatic toxicity. Congestive heart failure decreases hepatic blood flow by reducing cardiac output, which alters the extent of drug metabolism.

An alteration in production of the major drug-binding protein, albumin, can also alter the ratio of bound to unbound drug. Thus, a decrease in plasma albumin can increase the fraction of unbound (free) drug, which then becomes available to exert more of a pharmaceutical effect. The reverse is true when plasma albumin increases.

Genetic Factors

Drug action can vary as a result of genetic factors, a consideration discussed in more detail in the *Pharmacogenetics and Pharmacogenomics* chapter. Essentially, the metabolism rate for certain drugs can be slower or faster in some individuals based on genetic determinants. Some individuals are poor metabolizers of certain drugs because a specific CYP450 enzyme's activity is slower in those individuals compared to most persons in the general population.[41] Slower metabolism of drugs places these individuals at increased risk for adverse drug reactions and drug toxicity.

Lifestyle Behaviors

Lifestyle behaviors also are linked to pharmacodynamics and pharmacokinetics. For example, a woman who is prescribed a barbiturate—a drug that causes sedation and drowsiness—and who also ingests alcohol may have a drug–drug interaction that will enhance the sedative effect. Therefore, individuals need to be questioned frequently and directly with exacting questions such as "How much alcohol do you drink per day, and what do you drink?" rather than "Do you drink alcohol?" Women also need to be carefully questioned regarding self-medication with over-the-counter drugs, herbs, and dietary supplements. Any and all of these substances may interfere with a prescribed drug's effectiveness. For example, a pregnant woman with nausea and vomiting may self-medicate with the herb ginger. Generally in small and moderate doses, ginger may be helpful for some pregnant women; in pregnant women who are at high risk for hemorrhage, however, ginger inhibits platelet aggregation, thereby increasing their potential for bleeding.[42]

Individuals should also be questioned about their use of illegal substances. The use of illegal substances in addition to prescribed medications can result in acute toxicity. When a person who is taking heroin takes a barbiturate, for example, the combined sedative effect can result in a coma. Appropriate treatment is contingent upon the correct identification of the toxic substance. Illegal drug use is found in every age group, ethnicity, and socioeconomic status, so all individuals should be questioned about this practice.

The Role of Polypharmacy

Although there is no specific number of different drugs at which **polypharmacy** is universally defined, most studies have used five as the number of concurrently taken drugs that defines polypharmacy.[39] When a person is taking several medications due to multiple medical problems, the chance that a drug–drug interaction will occur increases. Because individuals may take several medications at a time and fail to report each one to their varied healthcare providers, the potential for drug–drug interactions can be high.[43]

Drug Adherence

Pharmacoadherence is the extent to which a person adheres to a medication regimen as mutually agreed upon with a healthcare professional.[44] Studies have found that 20% to 80% of individuals with chronic conditions requiring long-term pharmacologic regimens do not follow the prescribed regimen.[45] Measures of pharmacoadherence include direct, indirect, and subjective indexes. Direct measures may include biochemical assays as serum iron or total iron binding capacity levels for individuals with iron-deficiency anemia who are prescribed ferrous sulfate (Feosol). Indirect measures would include pill counts. Tailoring health education in accordance with the individual's culture, health literacy, and health numeracy may help improve pharmacoadherence. Health education is only one piece to this puzzle. Access to drugs and financial ability to pay for drugs can also adversely affect pharmacoadherance. Thus many factors need to be assessed when pharmacoadherance appears problematic.

Conclusion

According to the Institute of Medicine, in any 7-day period, 4 out of 5 adult individuals in the United States take prescription medications, over-the-counter medications, and

© Jones & Bartlett Learning, LLC. NOT FOR SALE OR DISTRIBUTION.

supplements.[46] In this organization's report *Preventing Medication Error: Quality Chasm Series*, medication errors were found to be a significant cause of morbidity and mortality. Providers of women's health care have a responsibility to understand the pharmacokinetics and pharmacodynamics of the drugs they order or administer. Multiple factors need to be considered, including age, gender, ethnicity, underlying health status, lifestyle behaviors that influence a drug's action, and effects. Routes and timing of drug administration vary depending on the drug and the woman's general health status. Monitoring for drug interactions with nutrients, herbs, and other drugs[46] and drug reactions is an important intervention. In addition, drug administration and responses vary across the lifespan, such that women who are pregnant, lactating, young, or elderly require special vigilance. Health education requires assessment of literacy, knowledge, and concerns, as well as the synergy of multidisciplinary healthcare members working together to provide the best care possible for women.

Resources

Organization	Description	Website
Indiana University School of Medicine	Drug interaction table of substrates, inhibitors, and inducers with links from the drug name to a PubMed list of citations that is continuously updated	http://medicine.iupui.edu/flockhart/table.htm
Concise Guide to Drug Interaction Principles for Medical Practice: Cytochrome P450s, UGTs, P-Glycoproteins	"Drugs" section in the Lexi-Complete PDA software package from Lexi-Comp; this PDA software includes a section on cytochrome P-450 enzyme activity for each drug narrative	
Merck Manual Online Medical Library	Overview of Pharmacokinetics and Overview of Pharmacodynamics: Articles that review the principles of pharmacokinetics with graphs and clinical correlates	www.merckmanuals.com/professional/clinical-pharmacology/pharmacokinetics/overview-of-pharmacokinetics
Interactive Clinical Pharmacology.org	Interactive colorful descriptions of many pharmacokinetic and pharmacodynamic concepts	www.icp.org.nz

References

1. Guittierrez K. *Pharmacotherapeutics.* 2nd ed. St. Louis: Saunders Elsevier; 2008: 44.
2. Berman A. Reducing medication errors through naming, labeling, and packaging. *J Med Syst.* 2004; 28:9-29.
3. Gavhane YN, Yadav AV. Loss of orally administered drugs in GI tract. *Saudi Pharm J.* 2012;20(4): 331-344.
4. Soderberg Lofda K, Andersson M, Gustafsson L. Cytochrome P450-mediated changes in oxycodone pharmacokinetics/pharmacodynamics and their clinical implications. *Drugs.* 2013;73:533-543.
5. Gao Y, Shao J, Jiang Z, et al. Drug enterohepatic circulation and distribution: constituents of systems pharmacokinetics. *Drug Discovery Today.* 2014;19(3):326-340.
6. Buxton ILO, Benet LZ. Pharmacokinetics: the dynamics of drug absorption, metabolism, and elimination. In: Brunton LL, Chabner B, Knollman B, eds. *Goodman & Gilman's the Pharmacological Basis of Therapeutics.* 12th ed. New York, NY: McGraw-Hill; 2011:17-40.
7. Meireles M, Martel F, Araújo J, et al. Characterization and modulation of glucose uptake in human blood–brain barrier model. *J Membr Biol.* 2013;246(9):669-677.
8. Smith B, Yogaratnam D, Levasseur-Franklin K, Forni A, Fong J. Introduction to drug pharmacokinetics in the critically ill patient. *Chest.* 2012;141(5):1327-1336.
9. Akhtar N, Ahad A, Khar RK, et al. The emerging role of P-glycoprotein inhibitors in drug delivery; a patent review. *Expert Opin Ther Pat.* 2011;21(4):561-576.
10. Corsini A, Bortolini M. Drug-induced liver injury: the role of drug metabolism and transport. *J Clin Pharmacol.* 2013;53(5):463-474.
11. Li F, Maag H, Alfredson T. Prodrugs of nucleoside analogues for improved oral absorption and tissue targeting. *J Pharm Sci.* 2008;97:1109-1134.
12. Krau SD. Cytochrome P450, part 1: what nurses really need to know. *Nurs Clin N Am.* 2013;48(4):671-680.
13. Wilkinson G. Drug metabolism and variability among patients in drug response. *N Engl J Med.* 2005;352(21):2211-2221.
14. Swen JJ, Nijenhuis M, de Boer A, et al. Pharmacogenetics: from bench to byte: an update of guidelines. *Clin Pharmacol Ther.* 2011;89(5):662-673.
15. Lynch T, Pice M. The effect of cytochrome P450 metabolism on drug response, interactions, and adverse effects. *Am Fam Phys* 2007;76:391-396.

© Jones & Bartlett Learning, LLC. NOT FOR SALE OR DISTRIBUTION.

16. Chan LN. Drug–nutrient interactions. *J Parenter Enteral Nutr.* 2013;37:450-459.
17. Pirmohamed M. Drug–grapefruit juice interactions. *BMJ.* 2013;346:f1.
18. Seden K, Dickinson L, Khoo S, Back D. Grapefruit–drug interactions. *Drugs.* 2010;70(18):2373-2407.
19. Chen J, Wilkinson J. The monoamine oxidase type B inhibitor rasagiline in the treatment of Parkinson disease: is tyramine a challenge? *J Clin Pharmacol.* 2012; 52:620-628.
20. Flockhart DA. Dietary restrictions and drug interactions with monoamine oxidase inhibitors: an update. *J Clin Psychiatry.* 2012;73(suppl 1):17-24.
21. Colalto C. Herbal interactions on absorption of drugs: mechanism of action and clinical risk assessment. *Pharmacol Res.* 2010;62:207-227.
22. Tsai H, Lin H, Simon Pickard A, Tsai H, Mahady G. Evaluation of documented drug interactions and contraindications associated with herbs and dietary supplements: a systematic literature review. *Int J Clin Pract.* 2012;66(11):1056-1078.
23. Kennedy DA, Seely D. Clinically based evidence of drug–herb interactions: a systematic review. *Expert Opin Drug Saf.* 2010;9(1):79-124.
24. Sahoo N, Manchikanti P, Dey S. Herbal drugs: standards and regulation. *Fitoterapia.* 2010;81:462-471.
25. Gardner DM, Shulman KI, Walker SE, Tailor SA. The making of a user friendly MAOI diet. *J Clin Psychiatry.* 1996;57:99-104.
26. Rahimi R, Abdollahi M. An update on the ability of St. John's wort to affect the metabolism of other drugs. *Expert Opin Drug Metab Toxicol.* 2012;8(6): 691-708.
27. Linde K, Berner MM, Kriston L. St John's wort for major depression. *Cochrane Database Syst Rev.* 2008;4:CD000448. DOI: 10.1002/14651858.CD000448.pub3.
28. Russo E, Scicchitano F, Whalley B, et al. *Hypericum perforatum*: pharmacokinetic, mechanism of action, tolerability, and clinical drug–drug interactions. *Phytother Res.* 2014;28(5):643-655.
29. Nieminen T, Hagelberg N, Saari T, et al. St John's wort greatly reduces the concentrations of oral oxycodone. *Eur J Pain.* 2010:14:854-859.
30. Murphy PA, Kern SE, Stanczyk FZ, Westhoff CL. Interaction of St. John's wort with oral contraceptives: effects on the pharmacokinetics of norethindrone and ethinyl estradiol, ovarian activity and breakthrough bleeding. *Contraception.* 2005;71(6):402-408.
31. Bunchorntavakul C, Reddy K. Review article: herbal and dietary supplement hepatotoxicity. *Aliment Pharmacol Ther.* 2013;37:3-17.
32. Li R, Barton HA, Varma MV. Prediction of pharmacokinetics and drug–drug interactions when hepatic transporters are involved. *Clin Pharmacokinet.* 2014; 53(8):659-678.
33. Hogg RC, Raggenbass M, Bertrand D. Nicotinic acetylcholine receptors: from structure to brain function. *Rev Physiol Biochem Pharmacol.* 2003;147:1-46.
34. Solinski HJ, Gudermann T, Breit A. Pharmacology and signalling of MAS-related G protein-coupled receptors. *Pharmacol Rev.* 2014;66(3):570-597.
35. Amezcua-Gutierrez MA, Cipres-Flores FJ, Trujillo-Ferrara JG, Soriano-Rusua MA. Clinical implications of recent insights into the structural biology of $beta_2$ adrenoreceptors. *Curr Drug Targets.* 2012; 13(10):1336-1346.
36. Witley H, Lindsey W. Sex-based differences in drug activity. *Am Fam Physician.* 2009;80(11):1254-1258.
37. Bruguerolle B. Clinical chronopharmacology in the elderly. *Chronobiol Int.* 2008;25(1):1-15.
38. Ohdo S, Koyanagi S, Matsunaga N, Hamdan A. Molecular basis of chronopharmaceutics. *J Pharm Sci.* 2011;100:3560-3576.
39. Zhao P, Xu P, Wan C, Wang Z. Evening versus morning dosing regimen drug therapy for hypertension. *Cochrane Database Syst Rev.* 2011;10:CD004184. DOI: 10.1002/14651858.CD004184.pub2.
40. Ayala DE, Ucieda R, Hermida RC. Chronotherapy with low-dose aspirin for prevention of complications in pregnancy. *Chronobiol Int.* 2013;30(1-2):260-279.
41. Samer CF, Lorenzini KI, Rollason V, Daali Y, Desmeules JA. Applications of CYP450 testing in the clinical setting. *Mol Diagn Ther.* 2013;17(3):165-184.
42. Liao YR, Leu YL, Chan YY, Kuo PC, Wu TS. Antiplatelet aggregation and vasorelaxing effects of the constituents of the rhizomes of *Zingiber officinale*. *Molecules.* 2012;17(8):8928-8937.
43. Hovstadius B, Petersson G. Factors leading to excessive polypharmacy. *Clin Geriatr Med.* 2012;28:159-172.
44. Chisholm-Burns MA, Spivey C. Pharmacoadherence: a new term for a significant problem. *Am J Health-Syst Pharm.* 2008;65:661-667.
45. Aronson J, Ferner RE. Clarification of terminology in drug safety. *Drug Safety.* 2005;28(10):851-870.
46. Institute of Medicine. *Preventing Medication Errors: Quality Chasm Series.* Washington, DC: Institute of Medicine; 2006.

© Jones & Bartlett Learning, LLC. NOT FOR SALE OR DISTRIBUTION.