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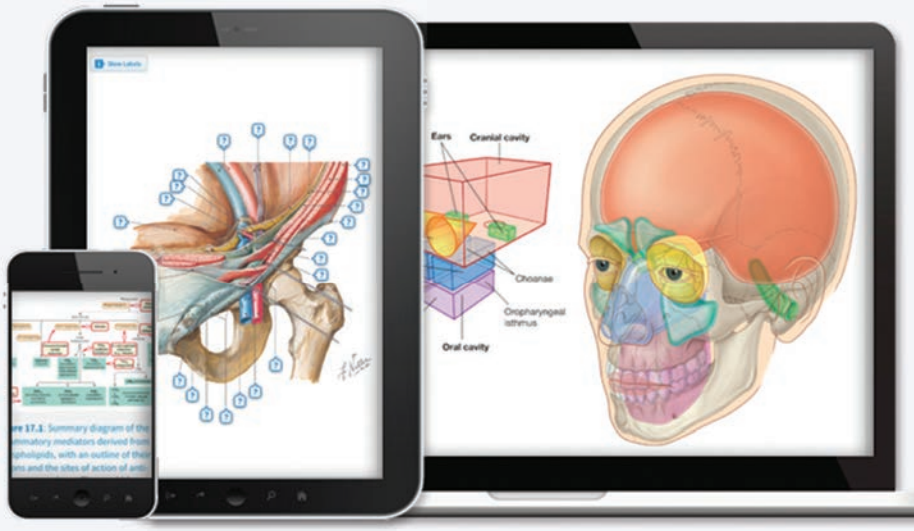


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# Brenner and Stevens' PHARMACOLOGY

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SIXTH EDITION

Craig W. Stevens, PhD
Professor of Pharmacology
Oklahoma State University
Center for Health Sciences
Tulsa, Oklahoma

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*Content Strategist:* Alexandra Mortimer
*Content Development Specialist:* Akanksha Marwah
*Publishing Services Manager:* Deepthi Unni
*Project Manager:* Aparna Venkatachalam
*Design Direction:* Margaret Reid

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# Preface

Medical pharmacology is primarily concerned with the mechanisms by which drugs treat disease processes, relieve symptoms, and counteract the molecular manifestations of pathological states. Pharmacology is also concerned with the factors that determine the time course of drug action, including drug absorption, distribution, metabolism, and excretion. Students are often overwhelmed by the vast amount of pharmacological information available today. This textbook provides the essential concepts and drug information that students need to be successful in their courses without an overwhelming amount of detail.

This text is primarily intended for students who are taking their first course in pharmacology, but it will also be useful for those who are preparing to take medical boards or licensing examinations. Because of the large number of drugs available today, this text emphasizes the general properties of drug categories and prototypical drugs. The chapters begin with a drug classification box to familiarize students with drug categories, subcategories, and specific drugs to be presented in the chapter. Additionally, all FDA-approved drugs are listed along with the emphasized drugs to enhance the value of this textbook as a reference volume.

In the four years since the publication of the previous edition of *Brenner and Stevens' Pharmacology*, major trends in the development and marketing of new medications and new formulations were apparent. First, there was an explosion of combination drugs released onto the market in recent years. This is a good thing, as there is often pharmacological synergy between combined agents, but also because patient compliance is greatly improved. It is easier to take one pill than two, or three, or four. The usual product combines two successful and effective single agents for the treatment of a disorder. These newly approved combination drugs are included in this 6th edition of *Brenner & Stevens' Pharmacology*.

Second, the market is flush with immunopharmacology drug products. Immunopharmacology products are rampant and apparent to both the physician and consumer by the numerous monoclonal antibody drugs touted in TV commercials. Pharmaceutical manufacturing of monoclonal antibody drugs that target enzymes, receptors, or other proteins is a rapidly growing sector of biologicals. Many therapeutic classes of pharmacological agents now have one or two drugs that work via antibodies or that target immune system factors. Because of the exponential growth of immunopharmacology drugs, a new Chapter 46 was added to close the book.

Third, the development and marketing of small molecule inhibitors skyrocketed in the last five years. Small molecule inhibitors were developed to go inside of cells and inhibit particular kinases or other enzymes and proteins. By contrast, more traditional drugs target receptor or enzymes on the cell membrane, like morphine acting on opioid receptors. Small molecule inhibitors are effective in many neoplastic (cancer) diseases and other pathological states with a well-defined molecular pathway. This new class of drugs with intracellular targets was added to Chapter 45.

The book has been meticulously organized to include extensive cross-referencing of many drugs that have more than one therapeutic use or multiple classifications. This will aid the reader in following a particular drug that is included in different chapters. Additionally, to aid the reader in drug recognition, drug names are followed by trade (brand) names in Small Caps Font. This helps because the trade name of many drugs are heavily advertised and the reader may already have some knowledge of their drug uses. As all medications are indexed under both their generic and brand names, this book is also a valuable reference for a quick review of drugs encountered in the reader's personal or professional life. However the student reader will bear in mind that for purposes of examination and boards, the unbranded generic drug name is exclusively used.

The book now in your hands was extensively revised for the 6th edition to include all new drugs on the market since the last edition (more than 200), and to exclude older drugs that were withdrawn from the market. Much ancillary drug information, such as chemical structures and unremarkable pharmacokinetics, was shortened or deleted. The figures that were retained were updated and new figures added, with an emphasis on illustrating drug mechanisms of action. A modern graphic style was developed for the figures to improve understanding and to entice the eye.

This new edition is sadly noted by the recent passing of Dr. George M. Brenner, my mentor, my friend, and co-author on previous editions of this textbook. George hired me 30 years ago as a young Assistant Professor of Pharmacology, collaborated on research projects, and encouraged my career as an academic scientist. Dr. Brenner had an encyclopedic knowledge of medications and his expertise is greatly missed. On another sad note, this book was written during the COVID-19 pandemic which took hundreds of thousands of lives due to infection with the SARS-CoV-2 virus. Although at the time of this writing there are no fully-approved FDA treatments for the pandemic virus, special sections on the emergency use drugs and developing vaccines are included in *Chapter 43* and *Chapter 46*.

I thank my numerous offspring and their mates for their constant love and attention which inspires me to undertake such massive projects like this textbook. I especially want to thank my OB/GYN wife, Dr. Timmeni L. Stevens, D.O., (*'the real doctor'*) for her help on *Chapter 34, Drugs Affecting Fertility and Reproduction*. I also appreciate the fine people at Elsevier, who bring it all together to produce the nicely designed textbook now in your hands. The interactions with

Alexandra Mortimer, Meghan Andress, and Kevin Travers were especially professional and pleasant. They seem to really enjoy their career and know what they are doing.

Finally, I am a pharmacologist who spent most of my career as a preclinical researcher using animals and cell cultures as models for understanding the human condition. I am not a physician or medical consultant. Therefore none of the following text should be taken as medical advice.

**Craig W. Stevens, PhD**
**Professor of Pharmacology**
**OSU-Center for Health Sciences**
**Tulsa, Oklahoma**

# Contents

Section

I

# PRINCIPLES OF PHARMACOLOGY

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CHAPTER 1

# Introduction to Pharmacology and Drug Names

## PHARMACOLOGY AND RELATED SCIENCES

**Pharmacology** is the **study of drugs and their effects** on living organisms, whether it be whole organisms, tissues, or cells. Pharmacology is a fundamental biomedical science that sprang to the forefront of modern medicine with a demonstrated success in using drugs to treat disease and save human lives. Pharmacology is also the scientific discipline that drives the international **pharmaceutical industry** to multibillion-dollar sales. This chapter reviews the history of pharmacology, identifies its major subdivisions, and introduces the types of drugs, formulations, and routes of administration.

### History and Definition of Pharmacology

Since the beginning of our species, people have treated pain and disease with substances derived from plants, animals, and minerals. However, the **science of pharmacology** is less than 150 years old, ushered in by the ability to isolate pure compounds from plants and the establishment of the scientific method.

Initially, drug use for aiding the sick consisted of crude plant and animal preparations given in a ritualistic manner to rid the body of the evil spirits believed to cause illness. Their effectiveness was probably due as much to beliefs or a placebo effect as it was to any medicinal property of the substances administered. Many cultures relied on a magicman or *shaman* to perform the healing rituals. Indeed, the Greek word *pharmakon*, from which the term *pharmacology* is derived, originally meant a magic charm for treating disease. Later, *pharmakon* came to mean a remedy or drug.

In the next phase of pharmacology, accrued knowledge from generations of medicinal rituals enabled people to correlate natural substances with treatment of particular diseases or symptoms. The **first effective drugs** were probably simple external preparations, such as cool mud for sunburn or a soothing mixture of plant leaves for an insect bite. The earliest known prescriptions, dating from 2100 BCE, included salves containing the spice thyme. In the ensuing centuries, people learned the **therapeutic value of natural products** through trial and error. By 1500 BCE, Egyptian prescriptions called for **castor oil, opium,** and other drugs still used today. In China, ancient scrolls from that time listed prescriptions for **herbal medicines** for more than 50 diseases. *Dioscorides*, a Greek army surgeon who lived in the 1st century, described more than 600 medicinal plants that he collected and studied as he traveled with the Roman army. *Susruta*, a Hindu healer, described the principles of Ayurvedic medicine in the 5th century. During the Middle Ages, Islamic physicians (most famously *Avicenna*) and Christian monks cultivated and studied the use of herbal medicines.

The current phase of pharmacology gradually evolved with important advances in **chemistry and physiology** that gave rise to modern pharmacology. At the same time, a more rational understanding of disease mechanisms provided a scientific basis for using drugs whose physiologic actions and effects were understood. The advent of pharmacology was particularly dependent on the isolation of pure drug compounds from natural sources and on the development of experimental physiology methods to study these compounds. The **isolation of morphine** from opium in 1804 was rapidly followed by the extraction of many other drugs from plant sources, providing a diverse array of pure drugs for **pharmacologic experimentation.** Advances in physiology allowed pioneers, such as François Magendie and Claude Bernard, to conduct some of the earliest pharmacologic investigations, including studies that localized the site of action of curare to the neuromuscular junction. The first medical school pharmacology laboratory was started by Rudolf Buchheim in Estonia. Buchheim and one of his students, Oswald Schmiedeberg, trained many other pharmacologists, including John Jacob Abel, who established the first pharmacology department at the University of Michigan in 1891 and is considered the father of American pharmacology.

The goal of pharmacology is to **understand the mechanisms by which drugs interact** with biologic systems to enable the rational use of effective agents in the diagnosis and treatment of disease. The success of pharmacology in this task has led to an explosion of new drug development, particularly in the past 50 years. Significant drug development includes the isolation and use of insulin for diabetes, the discovery of antimicrobial and antineoplastic drugs, and the advent of modern psychopharmacology. Recent advances in molecular biology, genetics, and computer-aided drug design suggest that new drug development and pharmacologic innovations will provide even greater advances in the treatment of medical disorders in the coming years.

The history of many significant events in pharmacology, as highlighted by selected Nobel Prize recipients, is presented in Table 1.1.

### Pharmacology and Its Subdivisions

**Pharmacology is the biomedical science** concerned with the interaction of chemical substances with living cells, tissues, and organisms. It is particularly concerned with the mechanisms by which drugs counteract the manifestations of disease and affect fertility. Pharmacology is not primarily focused on the methods of synthesis, isolation of drugs, or with the preparation of pharmaceutical products. The disciplines that deal with these subjects are described later.

Pharmacology is divided into two main subdivisions, **pharmacokinetics** and **pharmacodynamics.** The relationship between these subdivisions is shown in Fig. 1.1. Pharmacokinetics is concerned with the processes that determine the concentration of drugs in body fluids and tissues over time, including drug **absorption, distribution, metabolism,**

**TABLE 1.1 The Nobel Prize and the History of Pharmacology***

| PERSON(S) AND YEAR AWARDED | SIGNIFICANT DISCOVERY IN PHARMACOLOGY |
|---|---|
| Ilya Metchnikoff and Paul Ehrlich (1908) | First antimicrobial drugs *(magic bullet)* |
| Frederick Banting and John Macleod (1923) | Isolation and discovery of insulin and its application in the treatment of diabetes |
| Sir Henry Dale and Otto Loewi (1936) | Chemical transmission of nerve impulses |
| Sir Alexander Fleming, Ernst Chain, and Sir Howard Florey (1945) | Discovery of penicillin and its curative effect in various infectious diseases |
| Daniel Bovet (1957) | Antagonists that block biologically active amines, including the first antihistamine |
| Sir Bernard Katz, Ulf von Euler, and Julius Axelrod (1970) | Transmitters in the nerve terminals and the mechanism for storage, release, and inactivation |
| Sune Bergström, Bengt Samuelsson, and John Vane (1982) | Discovery of prostaglandins and the mechanism of action of aspirin that inhibits prostaglandin synthesis |
| Sir James Black, Gertrude Elion, and George Hitchings (1988) | Development of the first β-blocker, propranolol, and anticancer agents that block nucleic acid synthesis |
| Alfred Gilman and Martin Rodbell (1994) | Discovery of G proteins and the role of these proteins in signal transduction in cells |
| Robert Furchgott, Louis Ignarro, and Ferid Murad (1998) | Recognition of nitric oxide as a signaling molecule in the cardiovascular system |
| Arvid Carlsson, Paul Greengard, and Eric Kandel (2000) | Role of dopamine in schizophrenia and signal transduction in the nervous system leading to long-term potentiation |
| Robert J. Lefkowitz and Brian K. Kobilka (2012) | The structural basis of G protein–coupled receptor signaling |

*Selected from the list of recipients of the Nobel Prize for Physiology or Medicine, or the Nobel Prize for Chemistry; note that many other discoveries pertinent to pharmacology have been made by other Nobel Prize winners and that the original discovery was often made many years before the Nobel Prize was awarded.

and **excretion (ADME).** Pharmacodynamics is the study of the actions of drugs on target receptors and tissues. A shorthand way of thinking about it is that pharmacodynamics is what the drug does to the body, and pharmacokinetics is what the body does to the drug. Modern pharmacology is focused on the biochemical and molecular mechanisms by which drugs produce their physiologic effects and with the **dose-response relationship,** defined as the relationship between the concentration of a drug in a tissue and the magnitude of the tissue's response to that drug. Most drugs produce their effects by binding to protein **receptors** in target tissues, a process that activates a cascade of events known as **signal transduction.** Pharmacokinetics and pharmacodynamics are discussed in greater detail in Chapters 2 and 3, respectively.

## Toxicology

**Toxicology** is the study of **poisons** and **organ toxicity.** It focuses on the **harmful effects of drugs** and other chemicals and on the mechanisms by which these agents produce pathologic changes, disease, and death. As with pharmacology, toxicology is concerned with the relationship between the dose of an agent and the resulting tissue concentration and biologic effects that the agent produces. Most drugs have **toxic effects** at high enough doses and may have **adverse effects** related to toxicity at therapeutic doses.

## Pharmacotherapeutics

**Pharmacotherapeutics** is the medical science concerned with the **use of drugs in the treatment of disease.** Pharmacology provides a rational basis for pharmacotherapeutics by explaining the mechanisms and effects of drugs on the body and the relationship between dose and drug response. A cadre of research pharmacologists around the world does much preclinical research before drug candidates emerge. Human studies known as **clinical trials** are then used to determine the efficacy and safety of drug therapy in human subjects. The purpose, design, and evaluation of human drug studies are discussed in Chapter 4.

## Pharmacy and Related Sciences

**Pharmacy** is the science and profession concerned with the **preparation, storage, dispensing,** and **proper use** of drug products. Related sciences include pharmacognosy, medicinal chemistry, and pharmaceutical chemistry. **Pharmacognosy** is the study of drugs isolated from natural

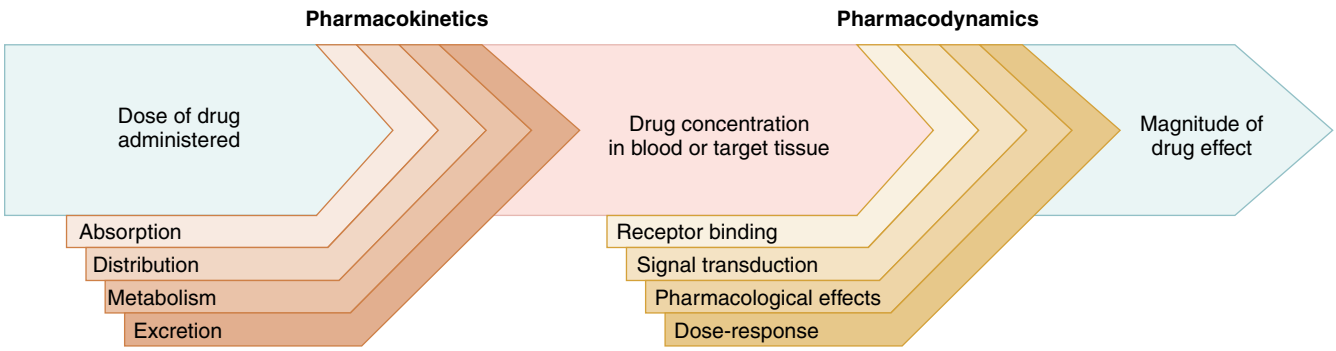


**Fig. 1.1** Relationship between pharmacokinetics and pharmacodynamics.

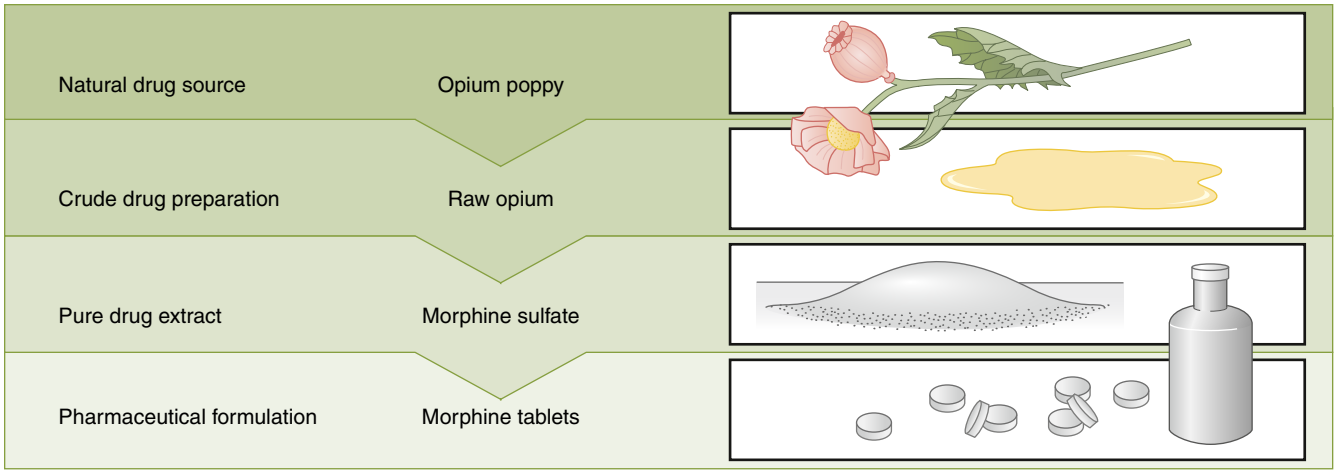


**Fig. 1.2** Types of drug preparations. A crude drug preparation retains most or all of the active and inactive compounds contained in the natural source from which it was derived. After a pure drug compound (e.g., morphine) is extracted from a crude drug preparation (in this case, opium), it is possible to manufacture pharmaceutical preparations that are suitable for administration of a particular dose to the patient.

sources, including plants, microbes, animal tissues, and minerals. **Medicinal chemistry** is a branch of organic chemistry that specializes in the design and chemical synthesis of drugs used in medicine. **Pharmaceutical chemistry,** or **pharmaceutics,** is concerned with the formulation and chemical properties of pharmaceutical products, such as tablets, liquid solutions and suspensions, and aerosols.

## DRUG SOURCES AND PREPARATIONS

A **drug** can be defined as a natural product, chemical substance, or pharmaceutical preparation intended for administration to a human or animal to diagnose or treat a disease. A drug can also be a *biologic* (e.g., a preparation of monoclonal antibodies). The word *drug* is derived from the French *drogue*, which originally meant dried herbs and was applied to herbs in the marketplace used for cooking rather than for any medicinal reason. Ironically, the medical use of the drug **marijuana,** a dried herb, is hotly debated in many societies nowadays. Drugs may be **hormones, neurotransmitters,** or **peptides** produced by the body; conversely, a **xenobiotic** is a drug produced outside the body, either synthetic or natural. A **poison** is a drug that can kill, whereas a **toxin** is a drug that can kill and is produced by a living organism. The terms **medication** and, used less frequently, **medicament** are synonymous with the word *drug*.

### Natural Sources of Drugs

Drugs have been obtained from plants, microbes, animal tissues, and minerals. Among the various types of drugs derived from plants are **alkaloids,** which are substances that contain nitrogen groups and produce an alkaline reaction in aqueous solution. Examples of alkaloids include morphine, cocaine, atropine, and quinine. **Antibiotics** have been isolated from numerous microorganisms, including *Penicillium* and *Streptomyces* species. **Hormones** are the most common type of drug obtained from animals, whereas **minerals** have yielded a few useful therapeutic agents, including the lithium compounds used to treat bipolar mental illness.

### Synthetic Drugs

Modern chemistry in the 19th century enabled scientists to synthesize new compounds and to modify naturally occurring drugs. Aspirin, barbiturates, and local anesthetics (e.g., **procaine**) were among the first drugs to be synthesized in the laboratory. Semisynthetic derivatives of naturally occurring compounds have led to new drugs with different properties, such as the morphine derivative **oxycodone.**

In some cases, new drug uses were discovered by accident when drugs were used for another purpose, or by actively screening a huge number of related molecules for a specific pharmacologic activity. Medicinal chemists now use molecular modeling software to discern the **structure-activity relationship,** which is the relationship among the drug molecule, its target receptor, and the resulting pharmacologic activity. In this way a virtual model for the receptor of a particular drug is created, and drug molecules that best fit the three-dimensional conformation of the receptor are synthesized. This approach has been used, for example, to design agents that inhibit angiotensin synthesis, treat hypertension, and inhibit the maturation of the human immunodeficiency virus (HIV).

### Drug Preparations

Drug preparations include **crude drug** preparations obtained from natural sources, **pure drug** compounds isolated from natural sources or synthesized in the laboratory, and **pharmaceutical preparations** of drugs intended for administration to patients. The relationship among these types of drug preparations is illustrated in Fig. 1.2.

#### Natural Sources of Drugs

The natural source of drugs is often a plant well known for its medicinal use and taken as is. Nicotine and marijuana plants are usually administered as drugs in their raw form as dried leaves. Other natural sources of drugs include *Amanita* mushrooms, which yield the plant alkaloid muscarine, and peyote cacti with the active ingredient of mescaline.

#### Crude Drug Preparations

Some **crude drug preparations** are made by drying or pulverizing a plant or animal tissue. Others are made by extracting substances from a natural product with the aid of hot water or a solvent such as alcohol. Familiar examples of crude drug preparations are **coffee** and **tea,** made from distillates of

the beans and leaves of *Coffea arabica* and *Camellia sinensis* plants, respectively, and **opium,** which is the dried juice of the unripe poppy capsule of the plant *Papaver somniferum*.

### Pure Drug Compounds

It is difficult to identify and quantify the pharmacologic effects of crude drug preparations because these products contain multiple ingredients with varying amounts from batch to batch. Therefore the development of methods to isolate **pure drug compounds from natural sources** was an important step in the growth of pharmacology and rational therapeutics. Frederick Sertürner, a German pharmacist, isolated the first pure drug from a natural source in 1804. He extracted and tested a potent **analgesic** agent from opium and named it **morphine,** from Morpheus, the Greek god of dreams. The subsequent isolation of many other drugs from natural sources provided pharmacologists with a number of pure compounds for study and characterization. One of the greatest medical achievements of the early 20th century was the isolation of insulin from the pancreas. This achievement led to the development of **insulin** preparations for treating **diabetes mellitus.**

### Pharmaceutical Preparations

Pharmaceutical preparations or dosage forms are drug products suitable for administration of a specific dose of a drug to a patient by a **particular route of administration.** Most of these preparations are made from pure drug compounds, but a few are made from crude drug preparations and sold as herbal remedies. By far, the most common formulation of drugs is for the **oral route** of administration, followed by formulations used for **injections.**

**Tablets and Capsules.** Tablets and capsules are the most common preparations for oral administration because they are suitable for mass production, are stable and convenient to use, and can be formulated to release the drug immediately after ingestion or to release it over a period of hours.

In the manufacture of tablets, a machine with a punch and die mechanism compresses a mixture of powdered drug and inert ingredients into a hard pill. The **inert ingredients** include specific components that provide bulk, prevent sticking to the punch and die during manufacture, maintain tablet stability in the bottle, and facilitate solubilization of the tablet when it reaches gastrointestinal fluids. These ingredients are called **fillers, lubricants, adhesives,** and **disintegrants,** respectively.

A tablet must disintegrate after it has been ingested, and then the drug must **dissolve in gastrointestinal fluids** before it can be absorbed into the circulation. Variations in the rate and extent of tablet disintegration and drug dissolution can give rise to differences in *bioavailability* of drugs from different tablet formulations (see Chapter 2).

Tablets may have various types of coatings. **Enteric coatings** consist of polymers that will not disintegrate in gastric acid but will break down in the more basic pH of the intestines. Enteric coatings are used to protect drugs that would otherwise be destroyed by gastric acid and to slow the release and absorption of a drug when a large dose is given at one time, for example, in the formulation of the antidepressant **fluoxetine,** called PROZAC WEEKLY.

**Sustained-release products,** or **extended-release products,** release the drug from the preparation over many hours. The two methods used to extend the release of a drug are **controlled diffusion** and **controlled dissolution.** With controlled diffusion, a rate-controlling membrane regulates release of the drug from the pharmaceutical product. Inert polymers gradually break down in body fluids creating a controlled dissolution. These polymers may be part of the tablet matrix, or they may be used as coatings over small pellets of drug enclosed in a capsule. In either case, the drug is gradually released into the gastrointestinal tract as the polymers dissolve.

Some products use **osmotic pressure** to provide a sustained release of a drug. These products contain an osmotic agent that attracts gastrointestinal fluid at a constant rate. The attracted fluid then forces the drug out of the tablet through a small laser-drilled hole (Fig. 1.3A).

**Capsules** are hard or soft gelatin shells enclosing a powdered or liquid medication. **Hard capsules** are used to enclose powdered drugs, whereas **soft capsules** enclose a drug in solution. The gelatin shell quickly dissolves in gastrointestinal fluids to release the drug for absorption into the circulation.

**Solutions and Suspensions.** Drug solutions and particle suspensions, the most common liquid pharmaceutical preparations, can be formulated for oral, parenteral, or other routes of administration. Solutions and suspensions provide a convenient method for administering drugs to pediatric and other patients who cannot easily swallow pills or tablets. However, they are less convenient than solid dosage forms because the liquid must be measured each time a dose is given.

Solutions and suspensions for oral administration are often sweetened and flavored to increase palatability. Sweetened aqueous solutions are called **syrups,** whereas sweetened aqueous-alcoholic solutions are known as **elixirs.** Alcohol is included in elixirs as a solvent for drugs that are not sufficiently soluble in water alone.

**Sterile solutions and suspensions** are available for **parenteral** administration with a needle and syringe or with an intravenous infusion pump. Many drugs are formulated as sterile powders for reconstitution with sterile liquids at the time the drug is to be injected, because the drug is not stable for long periods of time in solution. Sterile ophthalmic solutions and suspensions are suitable for administration with an eyedropper into the conjunctival sac.

**Skin Patches.** Transdermal skin patches are drug preparations in which the drug is slowly released from the patch for absorption through the skin into the circulation. Most skin patches use a **rate-controlling membrane** to regulate the diffusion of the drug from the patch (see Fig. 1.3B). Such devices are most suitable for potent drugs, which are therefore effective at relatively low doses and that have **sufficient lipid solubility** to enable skin penetration.

**Aerosols.** Aerosols are a type of drug preparation administered by inhalation through the **nose or mouth.** They are particularly useful for treating respiratory disorders because they deliver the drug directly to the site of action and may thereby minimize the risk of systemic side effects. Some aerosol devices contain the drug dispersed in a pressurized gas and are designed to deliver a precise dose each time they are activated by the patient. **Nasal sprays,** another type of aerosol preparation, can be used either to deliver drugs that have a localized effect on the nasal mucosa or to deliver

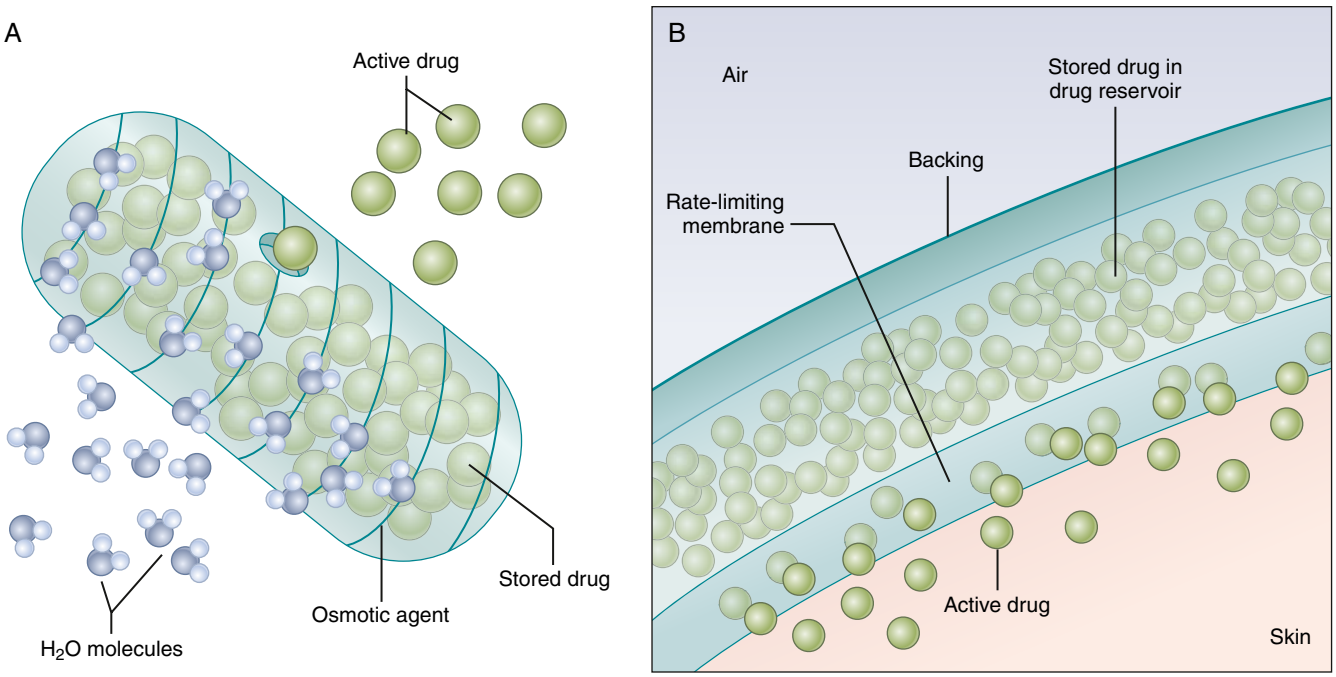


**Fig. 1.3** Mechanisms of sustained-release drug products. In the sustained-release tablet (A). Water is attracted by an osmotic agent in the tablet, and this forces the drug out through a small orifice. In the transdermal skin patch (B). The drug diffuses through a rate-controlling membrane and is absorbed through the skin into the circulation.

drugs that are absorbed through the mucosa and exert an effect on another organ. For example, **butorphanol,** an opioid analgesic, is available as a nasal spray (Stadol NS) for the treatment of pain.

**Ointments, Creams, Lotions, and Suppositories.** Ointments and creams are semisolid preparations intended for **topical application** of a drug to the skin or mucous membranes. These products contain an active drug incorporated into a vehicle (e.g., polyethylene glycol or petrolatum), which enables the drug to adhere to the tissue for a sufficient length of time to exert its effect. Lotions are liquid preparations often formulated as oil-in-water emulsions and are used to treat dermatologic conditions. Suppositories are products in which the drug is incorporated into a solid base that melts or dissolves at body temperature. Suppositories are used for **rectal, vaginal,** or **urethral administration** and may provide either localized or systemic drug therapy.

## ROUTES OF DRUG ADMINISTRATION

Some routes of drug administration, such as the **enteral** and common **parenteral** routes compared in Table 1.2, are intended to elicit systemic effects and are therefore called **systemic routes.** Other routes of administration, such as the inhalational route, can elicit either localized effects or systemic effects, depending on the drug being administered.

### Enteral Administration

The enteral routes of administration are those in which the drug is absorbed from the gastrointestinal tract. These include the **sublingual, buccal, oral,** and **rectal** routes.

In **sublingual administration,** a drug product is placed under the tongue. In **buccal administration,** the drug is placed between the cheek and the gum. Both the sublingual and the buccal routes of administration enable the rapid absorption of certain drugs and are not affected by first-pass drug metabolism in the liver. Drugs for sublingual and buccal administration are given in a relatively low dose and must have good solubility in water and lipid membranes. Larger doses might be irritating to the tissue and would likely be washed away by saliva before the drug could be absorbed. Two examples of drugs available for sublingual administration are **nitroglycerin** for treating ischemic heart disease and **hyoscyamine** for treating bowel cramps. **Fentanyl,** a potent opioid analgesic, is available in an oral transmucosal formulation (Actiq) with a lozenge on a stick ("lollypop") for rapid absorption from the buccal mucosa in the treatment of breakthrough cancer pain.

In medical orders and prescriptions, **oral administration** is designated as *per os* (PO), which means to administer "by mouth." The medication is swallowed, and the drug is absorbed from the stomach and small intestine. The oral route of administration is convenient, relatively safe, and the most economical. However, it does have some disadvantages. Absorption of orally administered drugs can vary widely because of the interaction of drugs with food and gastric acid and the varying rates of gastric emptying, intestinal transit, and tablet disintegration and dissolution. Moreover, some drugs are inactivated by the liver after their absorption from the gut, called **first-pass metabolism** (see Chapter 2), and oral administration is not suitable for use by patients who are sedated, comatose, or experiencing nausea and vomiting.

**Rectal administration** of drugs in suppository form can result in either a localized effect or a systemic effect. Suppositories are useful when patients cannot take medications by mouth, as in the treatment of nausea and vomiting. They can also be administered for localized conditions such as hemorrhoids. Drugs absorbed from the lower rectum undergo relatively little first-pass metabolism in the liver.

**TABLE 1.2 Advantages and Disadvantages of Four Common Routes of Drug Administration**

| ROUTE | ADVANTAGES | DISADVANTAGES |
|---|---|---|
| Oral | Convenient, relatively safe, and economical. | Cannot be used for drugs inactivated by gastric acid, for drugs with a large first-pass effect, or for drugs that irritate the gut. |
| Intramuscular | Suitable for suspensions and oily vehicles. Absorption is rapid from solutions and is slow and sustained from suspensions. | May be painful. Can cause bleeding if the patient is receiving an anticoagulant. |
| Subcutaneous | Suitable for suspensions and pellets. Absorption is similar to that in the intramuscular route but is usually somewhat slower. | Cannot be used for drugs that irritate cutaneous tissues or for drugs that must be given in large volumes. |
| Intravenous | Bypasses absorption to give an immediate effect. Allows for rapid titration of drug. Achieves 100% bioavailability. | Poses more risks for toxicity and tends to be more expensive than other routes. |

### Parenteral Administration

*Parenteral administration* refers to drug administration with a needle and syringe or with an intravenous infusion pump. The most commonly used parenteral routes are the **intravenous, intramuscular,** and **subcutaneous** routes.

**Intravenous administration** bypasses the process of drug absorption and provides the greatest reliability and control over the dose of drug reaching the systemic circulation. Because the drug is delivered directly into the blood, it has 100% **bioavailability** (see Chapter 2). The route is often preferred for administration of drugs with short half-lives and drugs whose dose must be carefully titrated to the physiologic response, such as agents used to treat hypotension, shock, and acute heart failure. The intravenous route is widely used to administer antibiotics and antineoplastic drugs to critically ill patients, as well as to treat various types of medical emergencies. The intravenous route is potentially the **most dangerous** because rapid administration of drugs by this route can cause serious toxicity.

**Intramuscular administration** and **subcutaneous administration** are suitable for treatment with drug solutions and particle suspensions. Solutions are absorbed more rapidly than particle suspensions, so suspensions are often used to extend the duration of action of a drug over many hours or days. Most drugs are absorbed more rapidly after intramuscular than after subcutaneous administration because of the greater circulation of blood to the muscle.

**Intrathecal administration** refers to injection of a drug through the thecal covering of the spinal cord and into the subarachnoid space. In cases of meningitis, the intrathecal route is useful in administering antibiotics that do not cross the blood-brain barrier. **Epidural administration,** common in labor and delivery, targets analgesics into the space above the dural membranes of the spinal cord.

Other, less common parenteral routes include **intra-articular administration** of drugs used to treat arthritis, **intradermal administration** for allergy tests, and **insufflation (intranasal administration)** for sinus medications.

### Transdermal Administration

Transdermal administration is the application of drugs to the skin for absorption into the circulation. Application can be via a **skin patch** or, less commonly, via an ointment. Transdermal administration, which bypasses first-pass metabolism, is a reliable route of administration for drugs that are effective when given at a relatively low dosage and that are highly soluble in lipid membranes. Transdermal skin patches slowly release medication for periods of time that typically range from 1 to 7 days. Two examples of transdermal preparations are the skin patches called **fentanyl transdermal** (DURAGESIC), used to treat severe chronic pain, and **nitroglycerin** ointment, used to treat heart failure and angina pectoris.

### Inhalational Administration

Inhalational administration can be used to produce either a localized or a systemic drug effect. A localized effect on the respiratory tract is achieved with drugs used to treat **asthma** or **rhinitis,** whereas a systemic effect is observed when a general anesthetic such as **sevoflurane** is inhaled.

### Topical Administration

Topical administration refers to the application of drugs to the **surface** of the body to produce a localized effect. It is often used to treat disease and trauma of the skin, eyes, nose, mouth, throat, rectum, and vagina.

## DRUG NAMES

A drug often has several names, including a **chemical** name, a **nonproprietary (generic)** name, and a **proprietary** name (or **trade** or **brand** name).

The **chemical name,** which specifies the chemical structure of the drug, uses standard chemical nomenclature. Some chemical names are short and easily pronounceable (e.g., the chemical name of aspirin is acetylsalicylic acid). Others are long and hard to pronounce owing to the size and complexity of the drug molecule. For most drugs, medicinal chemists primarily use the chemical name.

The **generic name** (nonproprietary name) is the type of drug name **most suitable for use by health care professionals.** In the United States, the generic names of drugs are the **United States Adopted Name** (USAN) designations. These designations, which are often derived from the chemical names of drugs, provide some indication of the class to which a particular drug belongs. For example, oxacillin can be easily recognized as a type of penicillin. The designations are selected by the USAN Council, which is a nomenclature committee representing the medical and pharmacy professions and the *United States Pharmacopeial Convention* (see Chapter 4). Students taking various board examinations including pharmacology (e.g., nursing boards, medical boards) will also be **most attentive to the generic** names of drugs.

The **brand name** (proprietary name, trade name) for a drug is the registered trademark belonging to a particular drug manufacturer and is used to designate a drug product marketed by that manufacturer. Heavily marketed brand names become common knowledge to patients, such as PROZAC and

VIAGRA. Many drugs are marketed under two or more brand names, especially after the manufacturer loses patent exclusivity. For example, ibuprofen (generic name) is marketed in the United States with the brand names of ADVIL, MOTRIN, and MIDOL. Drugs can also be marketed under their USAN designation. For these reasons, it is often less confusing and more precise to use the USAN rather than a brand name for a drug. However, the brand name may provide a better indication of the drug's pharmacologic or therapeutic effect. For example, DIURIL is a brand name for **chlorothiazide,** a diuretic; FLOMAX for **tamsulosin,** a drug used to increase urine flow; and MAXAIR for **pirbuterol,** a drug used to treat asthma.

### Generic Drug Substitution for Branded Drugs

When a new drug is developed and brought to market by a pharmaceutical manufacturer, the US Food and Drug Administration (FDA) approval comes with an exclusivity patent for the next 17 to 20 years. During this time, no other company can manufacture or sell the same drug. When the original drug loses exclusivity, generic drug manufacturers can file for a brief form of drug approval, limited to showing that the generic formulation exhibits the same **absorption** and **bioavailability** as the original, branded drug. Generic drugs are much cheaper because the second manufacturer does not have to recoup the costs of drug discovery, development, clinical trials, and the FDA new drug application.

Although the FDA does not regulate when to use generic drugs, most states have passed laws on **generic substitution.** Because use of generic medications instead of branded drugs can save millions of dollars in health care costs, some states mandate generic substitution without patient or physician approval, although physicians can override generic substitutions in some cases. Other states need the approval of the patient or physician to switch from a branded drug prescription to a generic substitute.

Both patient and physician misconceptions affect the underutilization of generic drugs. Scientific studies show that the overwhelming majority of generic medicines are **bioequivalent** to the branded, originator drug. The FDA has identified certain drugs that may be more dangerous to switch, called **narrow therapeutic index** (NTI) drugs, which may warrant further drug blood monitoring after a generic to branded drug substitution.

In this textbook, the generic name of a drug is given in the normal-sized font and its brand name in SMALL CAPS font. Note that not all generic drugs have a brand name counterpart.

## SUMMARY OF IMPORTANT POINTS

- The development of pharmacology was made possible by important advances in chemistry and physiology that enabled scientists to isolate and synthesize pure chemical compounds (drugs) and to design methods for identifying and quantifying the physiologic actions of the compounds.
- Pharmacology has two main subdivisions. Pharmacodynamics is concerned with the mechanisms of drug action and the dose-response relationship, whereas pharmacokinetics is concerned with the relationship between the drug dose and the plasma drug concentration over time.
- The sources of drugs are natural products (including plants, microbes, animal tissues, and minerals) and chemical synthesis. Drugs can exist as crude drug preparations, pure drug compounds, or pharmaceutical preparations used to administer a specific dose to a patient.
- The primary routes of administration are enteral (e.g., oral ingestion), parenteral (e.g., intravenous, intramuscular, and subcutaneous injection), transdermal, inhalational, and topical. Most routes produce systemic effects. Topical administration produces a localized effect at the site of administration.
- All drugs (pure compounds) have a nonproprietary name (or generic name, such as a USAN designation) and a chemical name. Some drugs also have one or more proprietary names (trade names or brand names) under which they are marketed by their manufacturer.

## Review Questions

1. Which route of drug administration is used with potent and lipophilic drugs in a patch formulation and avoids first-pass metabolism?
   (A) topical
   (B) sublingual
   (C) rectal
   (D) oral
   (E) transdermal
2. Which one of the following routes of administration does not have an absorption phase?
   (A) subcutaneous
   (B) intramuscular
   (C) intravenous
   (D) sublingual
   (E) inhalation
3. Which of the following correctly describes the intramuscular route of parenteral drug administration?
   (A) drug absorption is erratic and unpredictable
   (B) used to administer drug suspensions that are slowly absorbed
   (C) bypasses the process of drug absorption to achieve an immediate effect
   (D) cannot be used for drugs that undergo a high degree of first-pass metabolism
   (E) poses more risks than intravenous administration
4. An elderly patient has problems remembering to take her medication 3 times a day. Which one of the drug formulations might be particularly useful in this case?
   (A) extended release
   (B) suspension
   (C) suppository
   (D) skin patch
   (E) enteric coated
5. Which form of a drug name is most likely known by patients from exposure to drug advertisements?
   (A) nonproprietary name
   (B) British Approved Name
   (C) chemical name
   (D) generic name
   (E) trade name

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CHAPTER 2

# Pharmacokinetics or What the Body Does to the Drug

## OVERVIEW

Pharmacokinetics is the study of drug disposition in the body and focuses on the changes in **drug plasma concentration.** For any given drug and dose, the plasma concentration of the drug will rise and fall according to the rates of four processes: **absorption, distribution, metabolism,** and **excretion** (ADME). *Absorption* is the movement of drug from the site of administration to the bloodstream. The rate and extent of absorption are dependent on the physical characteristics of the drug and its formulation. *Distribution* is the process of a drug leaving the bloodstream and being distributed throughout the body, into the organs and tissues. **Metabolism,** also called **biotransformation,** is the process of converting a drug to one or more metabolites, primarily in the liver. **Excretion** is the removal of a drug or its metabolites from the body, primarily by the kidneys and urination. Sometimes the term **elimination** of a drug is used; this refers to the processes of metabolism and excretion combined. The relationship between these pharmacokinetic processes is explained more fully later and is shown in Fig. 2.1.

## DRUG ABSORPTION

*Drug absorption* refers to the **passage of drug molecules** from the site of administration into the circulation. The process of drug absorption applies to all routes of administration, except for the topical route, in which drugs are applied directly on the target tissue, and intravenous administration, in which the drug is given directly in the bloodstream. Drug absorption requires that drugs cross one or more layers of cells and cell membranes. Drugs injected into the subcutaneous tissue and muscle bypass the epithelial barrier and are more easily absorbed through spaces between capillary endothelial cells. In the gut, lungs, and skin, drugs must first be absorbed through a layer of epithelial cells that have tight junctions. For this reason, drugs face a greater **barrier** to absorption after oral administration than after parenteral administration.

### Processes of Absorption

Most drugs are absorbed by **passive diffusion** across a biologic barrier and into the circulation. The rate of absorption is proportional to the drug concentration gradient across the barrier and the surface area available for absorption at that site, known as **Fick's law**. Drugs can be absorbed passively through cells either by lipid diffusion or by aqueous diffusion. **Lipid diffusion** is a process by which the drug dissolves in the lipid components of the cell membranes. This process is facilitated by a high degree of lipid solubility of the drug. **Aqueous diffusion** occurs by passage through aqueous pores in cell membranes. Because aqueous diffusion is restricted to drugs with low molecular weights, many drugs are too large to be absorbed by this process.

A few drugs are absorbed by **active transport** or by **facilitated diffusion.** Active transport requires a **carrier molecule** and a form of **energy,** provided by hydrolysis of the terminal high-energy phosphate bond of adenosine triphosphate (ATP). Active transport can transfer drugs against a concentration gradient. For example, the antineoplastic drug **5-fluorouracil** undergoes active transport. Facilitated diffusion also requires a carrier molecule, but no energy is needed. Thus drugs or substances cannot be transferred against a concentration gradient but diffuse faster than without a carrier molecule present. Some cephalosporin antibiotics, such as **cephalexin,** undergo facilitated diffusion by an oligopeptide transporter protein located in intestinal epithelial cells.

### Effect of pH on Absorption of Weak Acids and Bases

Many drugs are weak acids or bases that exist in both ionized and nonionized forms in the body. Only the **nonionized form** of these drugs is sufficiently soluble in membrane lipids to cross cell membranes (Box 2.1). The ratio of the two forms at a particular site influences the **rate of absorption** and is also a factor in distribution and elimination.

The protonated form of a weak acid is nonionized, whereas the protonated form of a weak base is ionized. The ratio of the protonated form to the nonprotonated form of these drugs can be calculated using the **Henderson-Hasselbalch equation** (see Box 2.1). The $pK_a$ is the negative log of the ionization constant, particular for each acidic or basic drug. At a pH equal to the $pK_a$, **equal** amounts of the protonated and nonprotonated forms are present. If the pH is less than the $pK_a$, the protonated form predominates. If the pH is greater than the $pK_a$, the nonprotonated form predominates.

In the stomach, with a pH of 1, weak acids and bases are highly protonated. At this site, the nonionized form of weak acids ($pK_a$ = 3–5) and the ionized form of weak bases ($pK_a$ = 8–10) will predominate. Hence weak acids are more readily absorbed from the stomach than are weak bases. In the intestines, with a pH of 7, weak bases are also mostly ionized but much less so than in the stomach, and weak bases are absorbed more readily from the intestines than from the stomach.

However, weak acids can also be absorbed more readily from the intestines than from the stomach, despite their greater ionization in the intestines, because the intestines have a greater surface area than the stomach for absorption of the nonionized form of a drug, and this outweighs the influence of greater ionization in the intestines.

## DRUG DISTRIBUTION

Drugs are distributed to organs and tissues via the circulation, diffusing into interstitial fluid and into cells from the bloodstream. Most drugs are not uniformly distributed throughout total body water, and some drugs are restricted to the extracellular fluid or the plasma compartment. Drugs

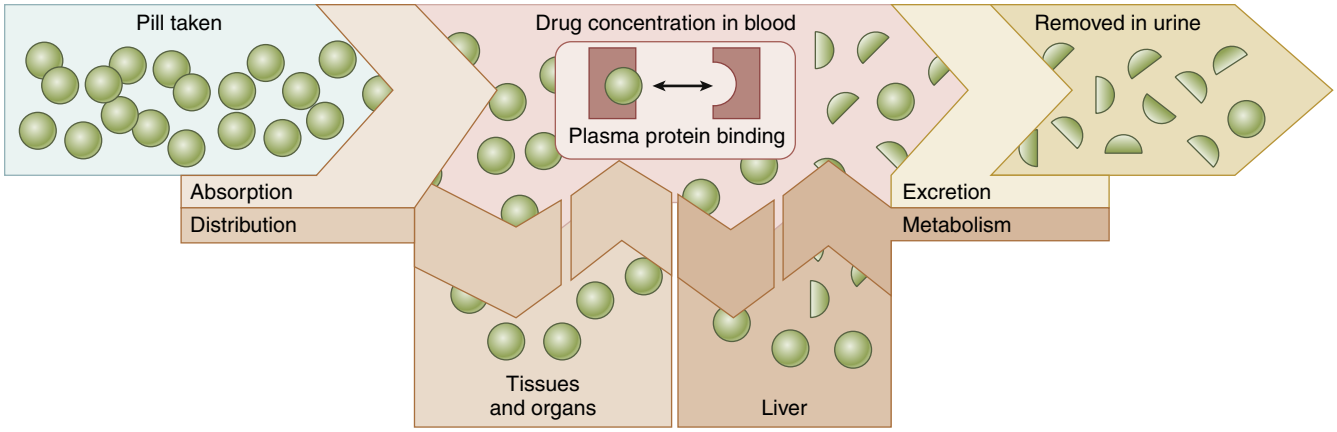


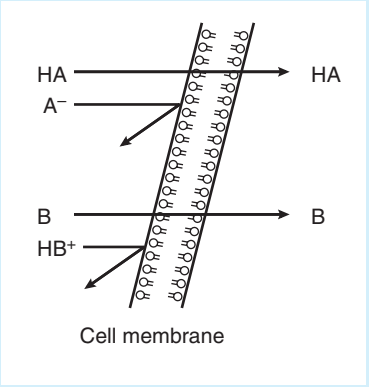

**Fig. 2.1** The absorption, distribution, biotransformation (metabolism), and excretion of a typical drug after its oral administration.

## BOX 2.1 EFFECT OF PH ON THE ABSORPTION OF A WEAK ACID AND A WEAK BASE

Weak **acids** (HA) donate a proton ($H^+$) to form anions ($A^-$), whereas **weak bases** (B) accept a proton to form cations ($HB^+$).

| | | | |
|---|---|---|---|
| HA | ⇌ | $H^+ + A^-$ | For weak acids, the protonated form is nonionized. |
| $B + H^+$ | ⇌ | $HB^+$ | For weak bases, the protonated form is ionized. |

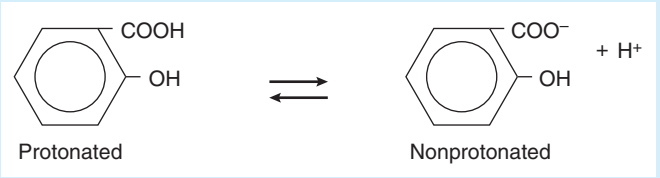
Only the **nonionized form** of a drug can readily penetrate cell membranes.



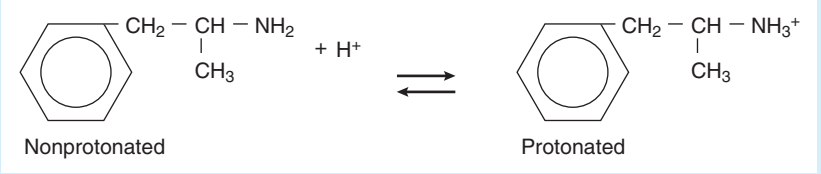

The **$pK_a$** of a weak acid or weak base is the **pH** at which there are equal amounts of the protonated form and the nonprotonated form. The **Henderson-Hasselbalch equation** can be used to determine the ratio of the two forms:

$$\log \frac{[\text{protonate form}]}{[\text{non protonate form}]} = pK_a - pH$$

For **salicylic acid,** which is a weak acid with a $pK_a$ of 3, log [HA]/[$A^-$] is 3 minus the pH. At a pH of 2, then, log [HA]/[$A^-$] = 3 – 2 = 1. Therefore [HA]/[$A^-$] = 10/1.




For **amphetamine,** which is a weak base with a $pK_a$ of 10, log [$HB^+$]/[B] is 10 minus the pH. At a pH of 8, then, log [$HB^+$]/[B] = 10 – 8 = 2. Therefore [$HB^+$]/[B] = 100/1.




The following are the ratios of the protonated form to the nonprotonated form at different pH levels:

| | | Salicylic acid | | | | | Amphetamine | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Protonated | | 10 | 1 | 1 | 1 | 1 | 1000 | 100 | 10 | 1 |
| | pH | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| Nonprotonated | | 1 | 1 | 10 | 100 | 1000 | 1 | 1 | 1 | 1 |

with sufficient lipid solubility can simply diffuse through membranes into cells. Other drugs are concentrated in cells by the phenomenon of **ion trapping,** which is described later. Drugs can also be actively transported into cells. For example, some drugs are actively transported into hepatic cells, where they undergo metabolism.

Opposing the distribution of drugs to tissues are a number of ATP-driven drug efflux pumps, known as **ABC transporters** (*ABC* is an acronym for "ATP-binding cassette"). The most studied of these proteins, called *permeability glycoprotein* or simply **P-glycoprotein (Pgp),** is expressed on the luminal side of endothelial cells lining the intestines, brain capillaries, and a number of other tissues. Drug transport in the blood-to-lumen direction leads to a secretion of various drugs into the intestinal tract, thereby serving as a detoxifying mechanism. Pgp also serves to exclude drugs from the brain. The Pgp proteins may exclude drugs from tissues throughout the body, including anticancer agents from tumors, leading to **chemotherapeutic drug resistance.** Inhibition of Pgp by amiodarone, erythromycin, propranolol, and other agents can increase tissue levels of these drugs and augment their pharmacologic effects (see Fig. 45.2).

### Factors Affecting Distribution

#### Organ Blood Flow

The rate at which a drug is distributed to various organs after a drug dose is administered depends largely on the proportion of **cardiac output** received by the organs. Drugs are rapidly distributed to highly perfused tissues, namely the brain, heart, liver, and kidney. This enables a rapid onset of action of drugs affecting these tissues. Drugs are distributed more slowly to less perfused tissues such as skeletal muscle and even more slowly to those with the lowest blood flow, such as skin, bone, and adipose (fat) tissue.

#### Plasma Protein Binding

Almost all drugs are reversibly bound to plasma proteins, primarily **albumin,** but also lipoproteins, glycoproteins, and *β*-globulins. The extent of binding depends on the affinity of a particular drug for protein-binding sites and ranges from less than 10% to as high as 99% of the plasma concentration. As the free (unbound) drug diffuses into interstitial fluid and cells, drug molecules dissociate from plasma proteins to maintain the equilibrium between free drug and bound drug. In general, **acidic drugs bind to albumin** and **basic drugs to glycoproteins** and ***β*-globulins.**

Plasma protein binding is **saturable,** and a drug can be displaced from binding sites by other drugs that have a high affinity for such sites. However, most drugs are not used at high enough plasma concentrations to occupy the vast number of plasma protein binding sites. There are a few agents that may cause drug interactions by competing for plasma protein binding sites, as highlighted in Chapter 4.

#### Molecular Size

Molecular size is a factor affecting the distribution of extremely large molecules, such as those of the anticoagulant **heparin.** Heparin is largely confined to the plasma compartment, although it does undergo some biotransformation in the liver.

**Lipid Solubility.** Lipid solubility is a major factor affecting the extent of drug distribution, particularly to the brain, where the **blood-brain barrier** restricts the penetration of polar and ionized molecules. The barrier is formed by tight junctions between the capillary endothelial cells and also by the glial cells that surround the capillaries, which inhibit the penetration of polar molecules into brain neurons.

## DRUG METABOLISM

**Drug metabolism** (biotransformation) and **excretion** are the two processes responsible for the decline of the plasma drug concentration over time. Both of these processes contribute to the **elimination** of active drug from the body. As discussed later in the chapter, **clearance** is a measure of the rate of elimination. Drug metabolism is the enzyme-catalyzed conversion of drugs to their metabolites. Most drug biotransformation takes place in the liver, but drug-metabolizing enzymes are found in many other tissues, including the gut, kidneys, brain, lungs, and skin.

### Role of Drug Biotransformation

The fundamental role of drug-metabolizing enzymes is to **inactivate** and **detoxify** drugs and other foreign substances (xenobiotics) that can enter the body. Drug metabolites are usually more water soluble than is the parent molecule, and therefore they are more readily excreted by the kidneys. No particular relationship exists between metabolism and pharmacologic activity. Some drug metabolites are active, whereas others are inactive. Many drug molecules undergo attachment of polar groups, a process called **conjugation,** for more rapid excretion. As a general rule, most conjugated drug metabolites are inactive, but a few exceptions exist.

### Formation of Active Metabolites

Many pharmacologically active drugs, such as the sedative-hypnotic agent **diazepam** (VALIUM), are biotransformed to active metabolites. Some agents, known as **prodrugs,** are administered as inactive compounds and then biotransformed to active metabolites. This type of agent is usually developed because the prodrug is better absorbed than its active metabolite. For example, the antiglaucoma agent **dipivefrin** (PROPINE) is a prodrug converted to its active metabolite, epinephrine, by corneal enzymes after topical ocular administration. Orally administered prodrugs, such as the antihypertensive agent **enalapril** (VASOTEC), are converted to their active metabolite by hepatic enzymes during their first pass through the liver.

### First-Pass Biotransformation

Drugs that are absorbed from the gut reach the liver via the hepatic portal vein before entering the systemic circulation (Fig. 2.2). Many drugs, such as the antihypertensive agent **felodipine** (PLENDIL), are extensively converted to inactive metabolites during their first pass through the gut wall and liver and have low **bioavailability** (see later) after oral administration. This phenomenon is called the **first-pass effect.** Drugs administered by the sublingual or rectal route undergo less first-pass metabolism and have a higher degree of bioavailability than do drugs administered by the oral route.

### Phases of Drug Biotransformation

Drug biotransformation can be divided into two phases, each carried out by a unique set of metabolic enzymes. In many cases, phase I enzymatic reactions create or unmask a

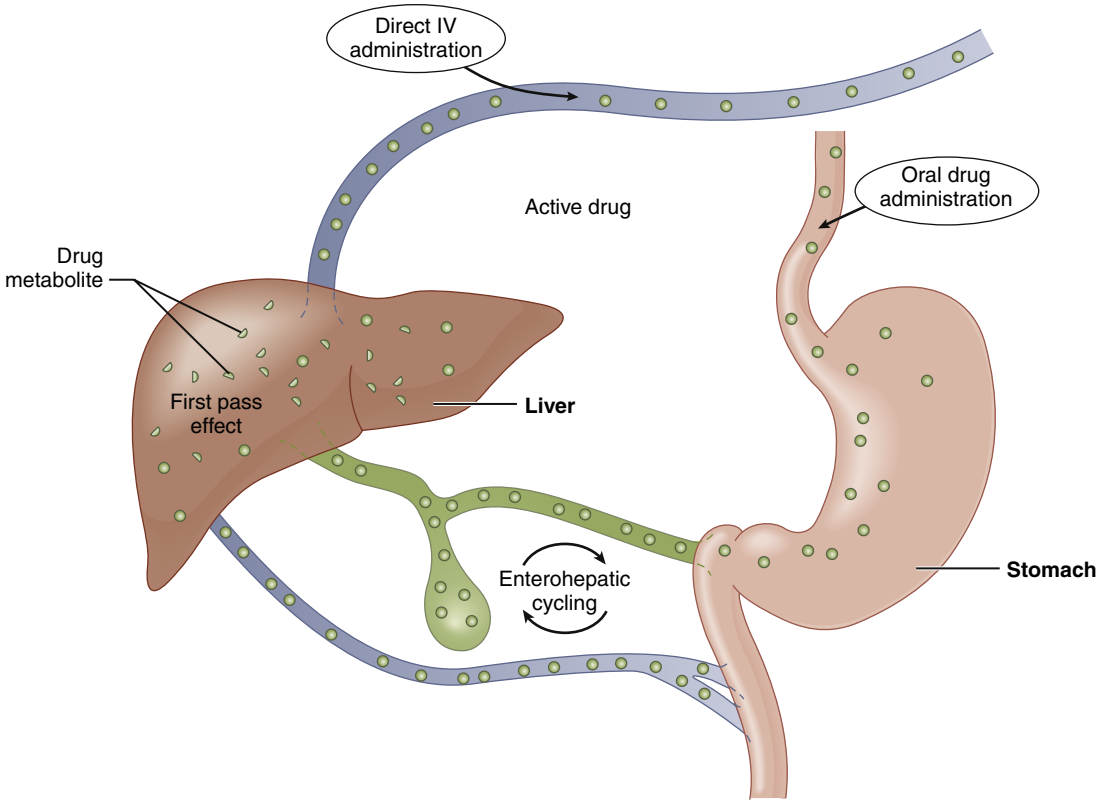



**Fig. 2.2** First-pass drug biotransformation. Drugs that are absorbed from the gut can be biotransformed by enzymes in the gut wall and liver before reaching the systemic circulation. This process lowers their degree of bioavailability. Enterohepatic cycling can occur when drugs and drug metabolites with molecular weights greater than 300 are excreted via the bile, stored in the gallbladder, delivered to the intestines by the bile duct, and then reabsorbed into the hepatic portal system. This process reduces the elimination of a drug and prolongs its half-life and duration of action in the body.

chemical group required for a phase II reaction. However, in some cases, drugs bypass phase I biotransformation and go directly to phase II. Although some phase I drug metabolites are pharmacologically active, most phase II drug metabolites are inactive.

## Phase I Biotransformation

Phase I biotransformation includes oxidative, hydrolytic, and reductive reactions (Fig. 2.3).

**Oxidative Reactions.** Oxidative reactions are the most common type of phase I biotransformation. They are catalyzed by enzymes isolated in the microsomal fraction of liver homogenates (the fraction derived from the endoplasmic reticulum) and by cytoplasmic enzymes.

The **microsomal cytochrome P450 (CYP) monooxygenase system** is a family of enzymes that catalyze the biotransformation of drugs with a wide range of chemical structures. The microsomal **monooxygenase reaction** requires the following: CYP (a hemoprotein); a flavoprotein reduced by nicotinamide adenine dinucleotide phosphate (NADPH), called *NADPH CYP reductase;* and membrane lipids in which the system is embedded. In the drug-oxidizing reaction, one atom of oxygen is used to form a hydroxylated metabolite of a drug, whereas the other atom of oxygen forms water when combined with electrons contributed by NADPH. The hydroxylated metabolite may be the end product of the reaction or serve as an intermediate that leads to the formation of another metabolite.

The most common chemical reactions catalyzed by CYP enzymes are aliphatic hydroxylation, aromatic hydroxylation, *N*-dealkylation, and *O*-dealkylation.

Many **CYP isozymes** have been identified and cloned, and their role in metabolizing specific drugs elucidated. Each isozyme catalyzes a different but overlapping spectrum of oxidative reactions. Most drug metabolism is catalyzed by three CYP families named *CYP1*, *CYP2*, and *CYP3*. The different CYP families are likely related by gene duplication, and each family is divided into subfamilies, also clearly related by homologous protein sequences. The **CYP3A** subfamily catalyzes more than half of all microsomal drug oxidation reactions.

Many drugs alter drug metabolism by inhibiting or inducing CYP enzymes, and **drug interactions** can occur when these drugs are administered concurrently with other drugs that are metabolized by CYP (see Chapter 4). Two examples of **inducers of CYP** are the barbiturate **phenobarbital** and the antitubercular drug **rifampin.** The inducers stimulate the transcription of genes encoding CYP enzymes, resulting in increased messenger RNA (mRNA) and protein synthesis. Drugs that induce CYP enzymes activate the binding of **transcription factors** to the promoter domains of CYP genes, increasing their rate of gene transcription.

A few drugs are oxidized by **cytoplasmic enzymes.** For example, **ethanol** is oxidized to aldehyde by alcohol dehydrogenase, and **caffeine** and the bronchodilator **theophylline** are metabolized by xanthine oxidase. Other cytoplasmic oxidases include **monoamine oxidase,** a site of action for some psychotropic medications.

**Hydrolytic Reactions.** Esters and amides are hydrolyzed by a variety of enzymes. These include cholinesterase and other plasma esterases that inactivate choline esters, local anesthetics, and drugs such as **esmolol** (Brevibloc), an

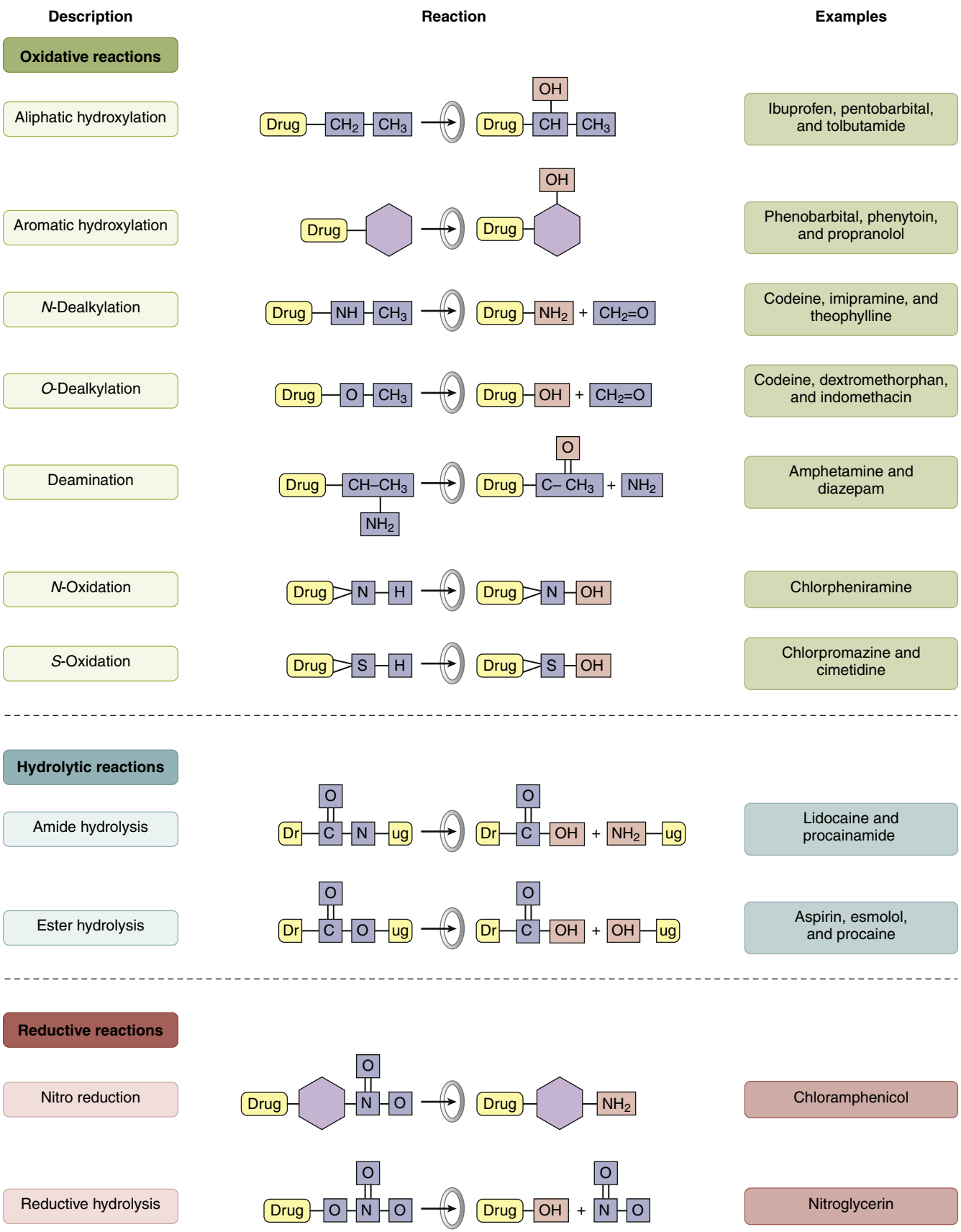



**Fig. 2.3** Phase I drug biotransformation. Many drugs are biotransformed by oxidative, hydrolytic, or reductive reactions and then undergo conjugation with endogenous substances. A few drugs bypass phase I reactions and directly enter phase II biotransformation.

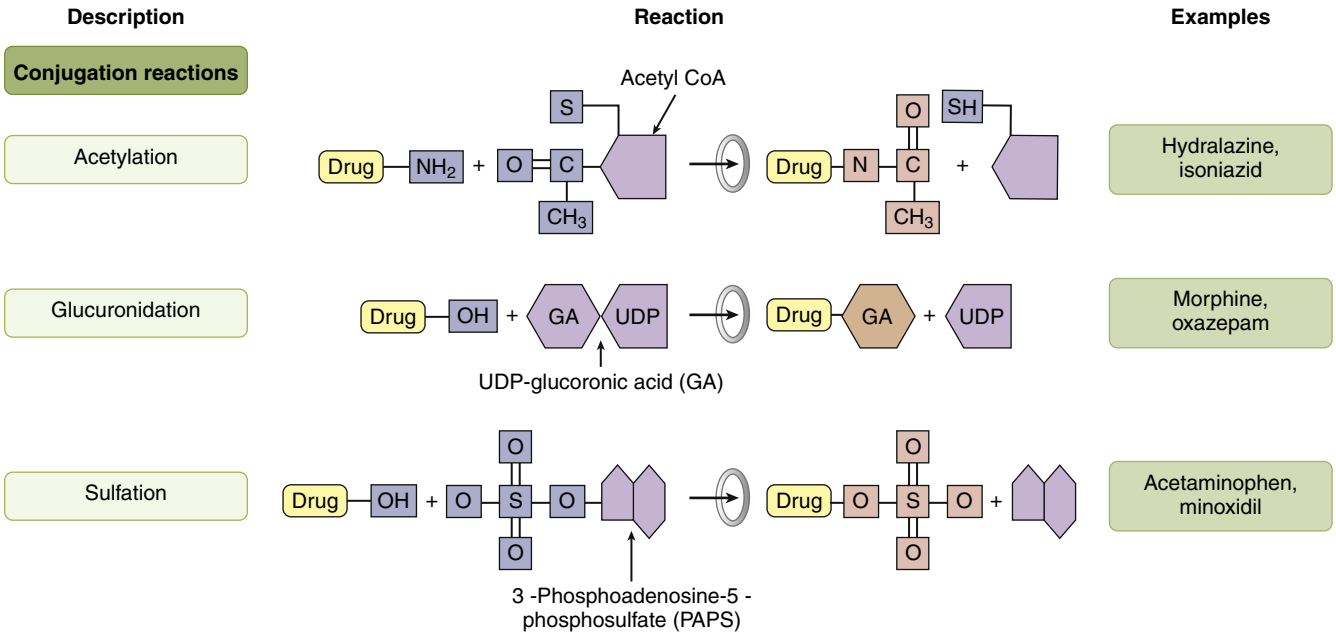



**Fig. 2.4** Phase II drug biotransformation. Many drugs undergo conjugation with endogenous substances as shown in the figure. *UDP,* Uridine diphosphate.

agent for the treatment of tachycardia that blocks cardiac $\beta_1$-adrenoceptors. There are few CYP enzymes that carry out hydrolytic reactions.

**Reductive Reactions.** Reductive reactions are less common than are oxidative and hydrolytic reactions. **Chloramphenicol,** an antimicrobial agent, and a few other drugs are partly metabolized by a hepatic nitroreductase, and this process involves CYP enzymes. **Nitroglycerin,** a vasodilator, undergoes reductive hydrolysis catalyzed by glutathione-organic nitrate reductase.

## Phase II Biotransformation

In phase II biotransformation, drug molecules undergo **conjugation reactions** with an endogenous substance such as **acetate, glucuronate, sulfate,** or **glycine** (Fig. 2.4). Conjugation enzymes, which are present in the liver and other tissues, join various drug molecules with one of these endogenous substances to form water-soluble metabolites that are more easily excreted. Except for microsomal **glucuronosyltransferases,** these enzymes are located in the cytoplasm. Most conjugated drug metabolites are pharmacologically inactive.

**Glucuronide Formation.** Glucuronide formation, the most common conjugation reaction, uses **glucuronosyltransferases** to conjugate a glucuronate molecule with the parent drug molecule.

**Acetylation.** Acetylation is accomplished by **N-acetyltransferase** enzymes that use acetyl coenzyme A (acetyl CoA) as a source of the acetate group.

**Sulfation.** **Sulfotransferases** catalyze the conjugation of several drugs, including the vasodilator **minoxidil** and the potassium-sparing diuretic **triamterene,** whose sulfate metabolites are pharmacologically active.

## Pharmacogenomics

Since the completion of the Human Genome Project, it is now fully realized that there is a great degree of individual variation, called **polymorphism,** in the genes coding for drug-metabolizing enzymes. Modern genetic studies were triggered by rare fatalities in children being treating for leukemia using the thiopurine agent 6-mercaptopurine (6-MP). It was discovered that the children died as a result of drug toxicity because they expressed a faulty variant of thiopurine methyltransferase, the enzyme that metabolizes 6-MP.

### Variations in Acetyltransferase Activity

Individuals exhibit slow or fast acetylation of some drugs because of genetically determined differences in *N*-acetyltransferase. Slow acetylators (SAs) were first identified by neuropathic effects of **isoniazid,** a drug to treat tuberculosis (see Chapter 41). These patients had higher plasma levels of isoniazid compared with other patients classified as rapid acetylators (RAs). The SA phenotype is autosomal recessive, although more than 20 allelic variants of the gene for *N*-acetyltransferase have been identified. In individuals with one wild-type enzyme and one faulty variant, an intermediate phenotype is observed. The **distribution** of these phenotypes varies from population to population. Approximately 15% of Asians, 50% of Whites and Africans, and more than 80% of Mideast populations have the SA phenotype. Other drugs that may cause toxicity in the SA patient are **sulfonamide antibiotics,** the antidysrhythmic agent **procainamide,** and the antihypertensive agent **hydralazine.**

### Variations in CYP2D6 and CYP2C19 Activity

Variations in oxidation of some drugs have been attributed to genetic differences in certain CYP enzymes. Genetic polymorphisms of CYP2D6 and CYP2C19 enzymes are well characterized, and human populations of "extensive metabolizers" and "poor metabolizers" have been identified. These differences are caused by more than 70 identified variants in the *CYP2D6* gene and more than 25 variants of the *CYP2C19* genes, resulting from point mutations, deletions, or additions; gene rearrangements; or deletion or

duplication of the entire gene. This gives rise to an increase, reduction, or complete loss of enzyme activity and to different levels of enzyme expression that result in **altered rates** of enzymatic reactions.

Most individuals are extensive metabolizers of CYP2D6 substrates, but 10% of Whites and a smaller fraction of Asians and Africans are poor metabolizers of substrates for CYP2D6. Psychiatric patients who are poor metabolizers of CYP2D6 drugs have been found to have a higher rate of adverse drug reactions than do those who are extensive metabolizers, because of higher psychotropic drug plasma levels. In addition, poor metabolizers of CYP2D6 drugs have a reduced ability to metabolize **codeine** to **morphine** sufficiently to obtain adequate pain relief when codeine is administered for analgesia.

Poor metabolizers of CYP2C19 substrates have higher plasma levels of proton pump inhibitors, such as **omeprazole** (PRILOSEC), whereas some extensive metabolizers of CYP2C19 drugs require larger doses of omeprazole to treat peptic ulcer.

### Other Variations in Drug Metabolism Enzymes

Approximately 1 in 3000 individuals exhibits a familial **atypical cholinesterase** that will not metabolize **succinylcholine,** a neuromuscular blocking agent, at a normal rate. Affected individuals are subject to prolonged apnea after receiving the usual dose of the drug. For this reason, patients should be screened for atypical cholinesterase before receiving succinylcholine.

There are many more **polymorphisms** in both phase I and phase II metabolic enzymes. With more than 30 families of drug-metabolizing enzymes, all with genetic variants, a major development in pharmacotherapy will be the individual tailoring of drug and dose to each patient's genomic identity.

## DRUG EXCRETION

Excretion is the removal of drug from body fluids and occurs primarily in the **urine.** Other routes of excretion from the body include in bile, sweat, saliva, tears, feces, breast milk, and exhaled air.

### Renal Drug Excretion

Most drugs are excreted in the urine, either as the parent compound or as a drug metabolite. Drugs are handled by the kidneys in the same manner as are endogenous substances, undergoing processes of glomerular filtration, active tubular secretion, and passive tubular reabsorption. The amount of drug excreted is the sum of the amounts filtered and secreted minus the amount reabsorbed. The relationship among these processes, the rate of drug excretion, and renal clearance is shown in Box 2.2.

### Glomerular Filtration

Glomerular filtration is the first step in renal drug excretion. In this process, the free drug enters the renal tubule as a dissolved solute in the plasma filtrate (see Box 2.2). If a drug has a large fraction bound to plasma proteins, as is the case with the anticoagulant **warfarin,** it will have a low rate of glomerular filtration.

### Active Tubular Secretion

Some drugs, particularly weak acids and bases, undergo active tubular secretion by transport systems located primarily in proximal tubular cells. This process is competitively inhibited by other drugs of the same chemical class. For example, the secretion of penicillins and other weak acids is inhibited by **probenecid,** an agent used to treat gout.

Active tubular secretion is not affected by plasma protein binding. This is a result of the equilibrium of free drug and bound drug, such that when free drug is actively transported across the renal tubule, this fraction of free drug is replaced by a fraction that dissociates from plasma proteins.

### Passive Tubular Reabsorption

The extent to which a drug undergoes passive reabsorption across renal tubular cells and into the circulation depends on the **lipid solubility** of the drug. Drug biotransformation facilitates drug elimination by forming polar drug metabolites that are not as readily reabsorbed as the less-polar parent molecules.

Most nonelectrolytes, including **ethanol,** are passively reabsorbed across tubular cells. Ionized weak acids and bases are not reabsorbed across renal tubular cells, and they are more rapidly excreted in the urine than are nonionized drugs that undergo passive reabsorption. The proportion of ionized and nonionized drugs is affected by **renal tubular pH,** which can be manipulated to increase the excretion of a drug after a drug overdose (Box 2.3).

### Biliary Excretion and Enterohepatic Cycling

Many drugs are excreted in the bile as the parent compound or a drug metabolite. Biliary excretion favors compounds with molecular weights greater than 300 and with both polar and lipophilic groups; smaller molecules are excreted only in negligible amounts. Conjugation, particularly with **glucuronate,** increases biliary excretion.

Numerous conjugated drug metabolites, including both the glucuronate and sulfate metabolites of steroids, are excreted in the bile. After the bile empties into the intestines, a fraction of the drug may be reabsorbed into the circulation and eventually return to the liver. This phenomenon is called **enterohepatic cycling** (see previous Fig. 2.2). Excreted conjugated drugs can be hydrolyzed back to the parent drug by intestinal bacteria, and this facilitates the drug's reabsorption. Thus biliary excretion eliminates substances from the body only to the extent that enterohepatic cycling is incomplete (i.e., when some of the excreted drug is not reabsorbed from the intestine).

### Other Routes of Excretion

Sweat and saliva are minor routes of excretion for some drugs. In pharmacokinetic studies, saliva measurements are sometimes used because the saliva concentration of a drug often reflects the intracellular concentration of the drug in target tissues.

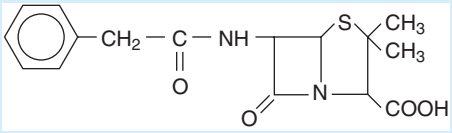
## QUANTITATIVE PHARMACOKINETICS

To derive and use expressions for pharmacokinetic parameters, the first step is to establish a mathematical model that accurately relates the plasma drug concentration to the rates of drug absorption, distribution, and elimination. The **one-compartment model** is the simplest model of drug disposition, but the **two-compartment model** provides a more accurate representation of the pharmacokinetic behavior of many drugs (Fig. 2.5). With the one-compartment model, a

## BOX 2.2 THE RENAL EXCRETION AND CLEARANCE OF A WEAK ACID, PENICILLIN G

### DESCRIPTION AND CHEMICAL STRUCTURE

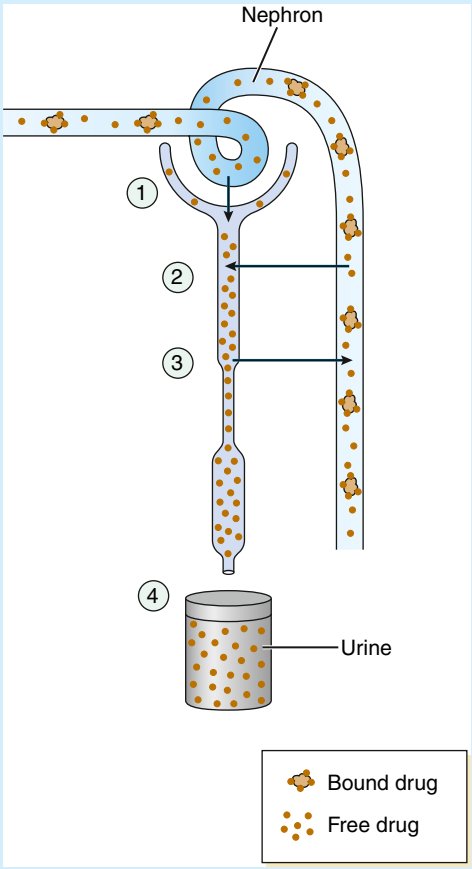
Penicillin G (benzylpenicillin) is an example of a weak acid. It has a **$pK_a$** of 2.8 and is primarily excreted via renal tubular secretion. Approximately 60% of penicillin G is bound to plasma proteins. The pharmacokinetic calculations that follow are based on a urine **pH** of 5.8, a **plasma drug concentration** of 3 mg/mL, a **glomerular filtration rate** of 100 mL/min, and a **measured drug excretion rate** of 1200 mg/min. Because 40% of penicillin G is free (unbound), the **free drug plasma concentration** is 0.4 × 3 mg/mL = 1.2 mg/mL.




### RENAL EXCRETION

The discussion and accompanying figure illustrate the relationship among the rates of glomerular filtration, active tubular secretion, passive tubular reabsorption, and excretion.

1. **Filtration.** The **drug filtration rate** is calculated by multiplying the glomerular filtration rate by the free drug plasma concentration: 100 mL/min × 1.2 mg/mL = 120 mg/min.
2. **Secretion.** The **drug secretion rate** is calculated by subtracting the drug filtration rate from the drug excretion rate: 1200 mg/min – 120 mg/min = 1080 mg/min. This amount indicates that 90% of the drug's excretion occurs by the process of tubular secretion.
3. **Reabsorption.** The ratio of the nonionized form to the ionized form of the drug in the urine is equal to the antilog of the $pK_a$ minus the pH: antilog of 2.8 – 5.8 = antilog of –3 = 1:1000. Because most of the drug is ionized in the urine, the **drug reabsorption rate** is probably less than 1 mg/min.
4. **Excretion.** The drug excretion rate was initially given as 1200 mg/min. It was determined by measuring the drug concentration in urine and multiplying it by the urine flow rate. Note that the drug excretion rate is equal to the drug filtration rate (120 mg/min) plus the drug secretion rate (1080 mg/min) minus the drug reabsorption rate (<1 mg/min).




### RENAL CLEARANCE

Renal clearance is calculated by dividing the excretion rate (1200 mg/min) by the plasma drug concentration (3 mg/mL). The result is 400 mL/min, which is equal to 24 L/h.

## BOX 2.3 URINE ACIDIFICATION AND ALKALINIZATION IN THE TREATMENT OF DRUG OVERDOSE

If a drug or other compound is a weak acid or base, its degree of ionization and rate of renal excretion will depend on its $pK_a$ and on the pH of the renal tubular fluid. The rate of excretion of a **weak acid** can be accelerated by **alkalinizing the urine,** whereas the rate of excretion of a **weak base** can be accelerated by **acidifying the urine.** These procedures have been used to enhance the excretion of drugs and poisons, but they are not without risk to the patient, and their benefits have been established for only a few drugs.

To make manipulation of the urine pH worthwhile, a drug must be excreted to a large degree by the kidneys. The short-acting barbiturates (e.g., secobarbital) are eliminated almost entirely via biotransformation to inactive metabolites, so modification of the urine pH has little effect on their excretion. In contrast, phenobarbital is excreted to a large degree by the kidneys, so urine alkalinization is useful in treating an overdose of this drug. Urine acidification to enhance the elimination of weak bases (e.g., amphetamine) has been largely abandoned because it does not significantly increase the elimination of these drugs and poses a serious risk of metabolic acidosis.

In cases involving an overdose of aspirin or other salicylate, alkalinization of the urine produces the dual benefits of increasing drug excretion and counteracting the metabolic acidosis that occurs with serious aspirin toxicity. For patients with phenobarbital overdose or herbicide 2,4-dichlorophenoxyacetic acid poisoning, alkalinization of the urine is also helpful; this is accomplished by administering sodium bicarbonate intravenously every 3 to 4 hours to increase the urinary pH to 7 to 8.

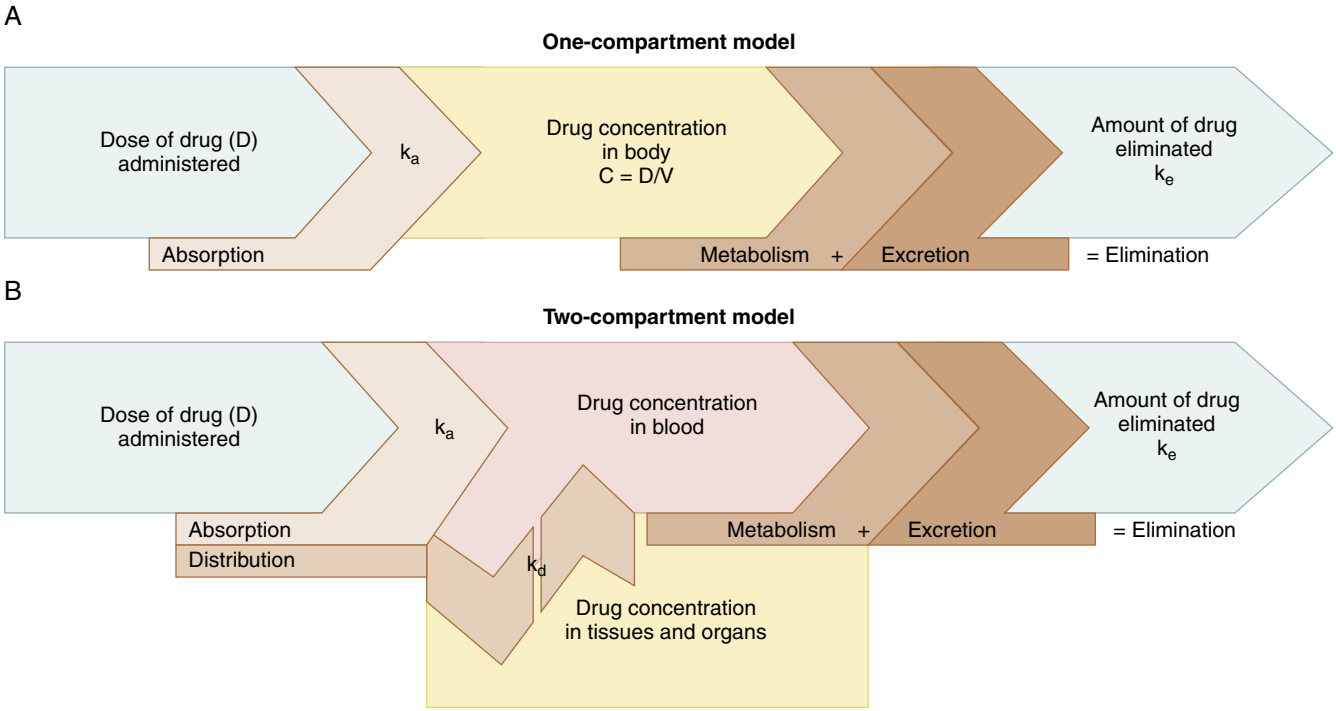



**Fig. 2.5** Two models of the processes of drug absorption, distribution, and elimination: $k_a$, $k_d$, and $k_e$ are the rate constants, representing the fractional completion of each process per unit of time. (A) In the one-compartment model, the drug concentration at any time, C, is the amount of drug in the body at that time, D, divided by the volume of the compartment, V. Thus D is a function of the dose administered and the rates of absorption and elimination represented by $k_a$ and $k_e$, respectively. (B) In the two-compartment model, the drug concentration in the central compartment (the blood) is a function of the dose administered and the rates of drug absorption, distribution to the peripheral compartment (the tissues), and elimination from the central compartment.

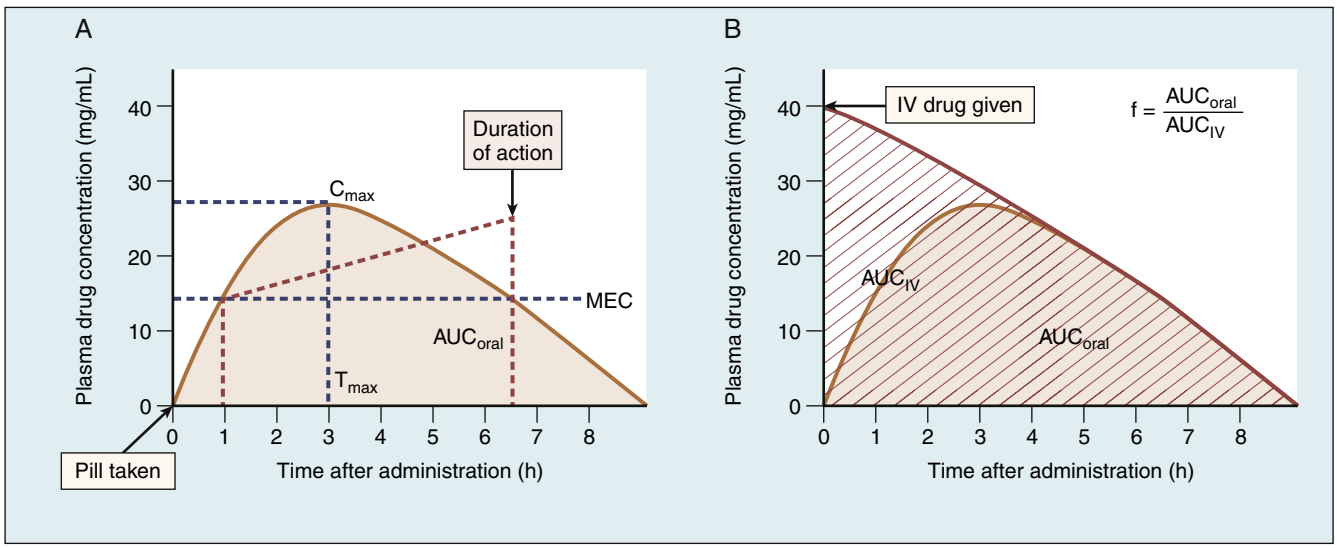



**Fig. 2.6** Plasma drug concentration and drug bioavailability. The plasma drug concentration curve for a single dose of a drug given orally (A) shows maximum concentration ($C_{max}$), the time needed to reach the maximum ($T_{max}$), the minimum effective concentration (*MEC*), the duration of action, and the area under the curve (*AUC*). (B) To determine bioavailability, F, the AUC of the $AUC_{oral}$ is divided by the AUC of the intravenously administered drug, $AUC_{IV}$.

drug undergoes absorption into the blood according to the rate constant $k_a$ and elimination from the blood with the rate constant $k_e$. In the two-compartment model, drugs are absorbed into the central compartment (blood), distributed from the central compartment to the peripheral compartment (the tissues), and eliminated from the central compartment. Regardless of the model used, rate constants can be determined for each process and used to derive expressions for other pharmacokinetic parameters, such as the **elimination half-life (t½)** of a drug. In this section, the most important parameters of pharmacokinetics are explained in greater detail.

## Drug Plasma Concentration Curves

Fig. 2.6A shows a standardized **drug plasma concentration curve** over time after oral administration of a typical drug.

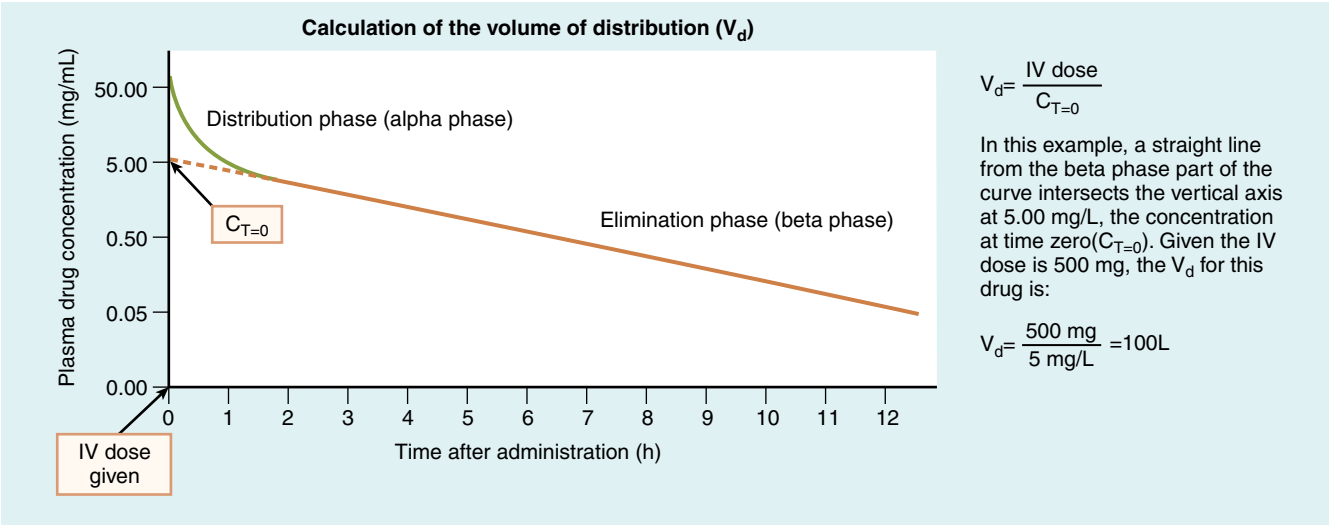



**Fig. 2.7** Calculating the volume of distribution ($V_d$) of a drug. The graph provides an example of how the $V_d$ is calculated. A dose of 500 mg was injected intravenously at time zero, and plasma drug concentrations were measured over time. The terminal elimination curve ($\beta$ elimination phase) was extrapolated back to time zero to determine that the plasma drug concentration at time zero, $C_{T=0}$, was 5 mg/L. Then the $V_d$ was calculated by dividing the dose by the $C_{T=0}$. In this case the result was 100 L.

The y-axis is a linear scale of drug plasma concentration, often expressed in micrograms per milliliter or milligrams per liter, and the x-axis is a scale of time, usually expressed in hours. Parameters of the plasma drug concentration curve are the **maximum concentration (Cmax),** the time needed to reach the maximum **(Tmax),** the **minimum effective concentration (MEC),** and the **duration of action.** A measure of the total amount of drug during the time course is given by the **area under the curve (AUC).** These measures are useful for comparing the **bioavailability** of different pharmaceutical formulations or of drugs given by different routes of administration.

## Bioavailability

**Bioavailability** is defined as the **fraction (F)** of the administered dose of a drug that reaches the systemic circulation in an active form. As shown in Fig. 2.6B, the oral bioavailability of a particular drug is determined by dividing the AUC of an orally administered dose of the drug ($AUC_{oral}$) by the AUC of an intravenously administered dose of the same drug ($AUC_{IV}$). By definition, an intravenously administered drug has 100% bioavailability. The bioavailability of drugs administered intramuscularly or via other routes can be determined in the same manner as the bioavailability of drugs administered orally.

The bioavailability of orally administered drugs is of particular concern because it can be reduced by many pharmaceutical and biologic factors. Pharmaceutical factors include the **rate and extent of tablet disintegration** and drug dissolution. Biologic factors include the effects of food, which can sequester or inactivate a drug; the effects of gastric acid, which can inactivate a drug; and the effects of gut and liver enzymes, which can metabolize a drug during its absorption and first pass through the liver. The CYP3A4 isozyme found in intestinal enterocytes and hepatic cells is a particularly important catalyst of first-pass drug metabolism. CYP3A4 works in conjunction with Pgp (described in the section discussing drug distribution), as the 3A4 isozyme located in enterocytes inactivates drugs transported into the intestinal lumen by Pgp.

## Volume of Distribution

The volume of distribution **($V_d$)** is defined as the volume of fluid in which a dose of a drug would need to be dissolved to have the **same concentration** as it does in plasma. The $V_d$ does not necessarily represent the volume in a particular body fluid compartment. Instead, the $V_d$ is an apparent volume that represents the relationship between the dose of a drug and the resulting plasma concentration of the drug, to account for the immediate distribution of the drug out of the blood after absorption.

### Calculation of the Volume of Distribution

After intravenous drug administration, the plasma drug concentration falls rapidly at first as the drug is distributed from the central compartment to the peripheral compartment. The $V_d$ is calculated by dividing the dose of a drug given intravenously by the plasma drug concentration immediately after the initial or *alpha* ($\alpha$) distribution phase. As shown in Fig. 2.7, this drug concentration can be determined by extrapolating the plasma drug concentration back to time zero from the linear part of the latter or *beta* ($\beta$) elimination phase. Note that the y-axis in this case is plotted on a **log scale** so that the exponential decay curve of the elimination phase is converted to a straight line. The plasma **drug concentration at time zero ($C_{T=0}$)** represents the plasma concentration of a drug that would be obtained if it were instantaneously dissolved in its $V_d$. The equation for calculating $V_d$ is rearranged to determine the dose of a drug required to establish a specified plasma drug concentration and to calculate a loading dose (Box 2.4).

### Interpretation of the Volume of Distribution

Although the $V_d$ does not correspond to an actual body fluid compartment, it does provide a measure of the extent of distribution of a drug. A low $V_d$ that approximates plasma volume or extracellular fluid volume usually indicates that the drug's distribution is restricted to a particular compartment (the plasma or extracellular fluid). The anticoagulant **warfarin** has a $V_d$ of approximately 8 L, which reflects a high degree of plasma protein binding. When the $V_d$ of a drug

## BOX 2.4 DRUG DOSAGE CALCULATIONS

### LOADING DOSE

The loading dose, or priming dose, of a drug is determined by multiplying the **volume of distribution** ($V_d$) of the drug by the **desired plasma drug concentration** (desired C). (This information can be found in the medical literature.) For example, for theophylline, the estimated $V_d$ for an adult weighing 70 kg is 35 L, and the desired C is 15 mg/L. The calculation is as follows:

$$\text{Loading dose} = V_d \times C$$
$$= 35\ \text{L} \times 15\ \text{mg/L}$$
$$= 525\ \text{mg}$$

As is discussed in Chapter 4 (see Table 4.5), the patient's age can affect the $V_d$ and therefore should be considered in determining the appropriate loading dose for a particular patient.

### MAINTENANCE DOSE

Calculations of the maintenance dose must take into consideration the **intended frequency of drug administration.** With intermittent administration, the fluctuations in C increase as the dosage interval increases. A twofold fluctuation in C will occur when the dosage interval is equal to the drug's half-life. This is because the C will fall 50% between doses. For many drugs, the half-life is a convenient and acceptable dosage interval.

The maintenance dose is designed to establish or maintain a **desired steady state C.** The amount of drug to be given is based on the principle that at the steady state, the rate of drug administration equals the rate of drug elimination. The rate of elimination is equal to the clearance multiplied by the steady-state drug concentration. For example, if the steady-state gentamicin concentration is 2 mg/L and the clearance rate for gentamicin is 100 mL/min (0.1 L/min), then the elimination rate is 0.1 L/min × 2 mg/L = 0.2 mg/min. If the drug is to be administered every 8 hours, then the dosage would be calculated as follows:

$$\text{Maintenance dose} = \text{Hourly rate} \times \text{dosage interval in hours}$$
$$= 0.2\ \text{mg/min} \times 60\ \text{minutes in an hour} \times 8\ \text{hours}$$
$$= 96\ \text{mg every 8 hours}$$

If a drug is to be administered orally, the calculated dose must be divided by the fractional bioavailability to determine the administered dose.

### DOSAGE ADJUSTMENT USING PHARMACOKINETIC VALUES

First, choose the target C and administer the initial dose on the basis of the standard published values (general population values) for clearance or $V_d$. Second, measure the patient's plasma drug levels and calculate the patient's $V_d$ and clearance. Third, revise the dosage based on the patient's $V_d$ and clearance.

is equivalent to total body water (approximately 40 L, as occurs with ethanol), this usually indicates that the drug has reached the intracellular fluid as well.

Some drugs have a $V_d$ that is much larger than total body water. A large $V_d$ may indicate that the drug is concentrated intracellularly, with a resulting low concentration in the plasma. Many weak bases, such as the antidepressant **fluoxetine** (PROZAC), have a large $V_d$ (40–55 L) because of the phenomenon of intracellular **ion trapping.** Weak bases are less ionized within plasma than they are within cells because intracellular fluid usually has a lower pH than extracellular fluid. After a weak base diffuses into a cell, a larger fraction is ionized in the more acidic intracellular fluid. This restricts its diffusion out of a cell and results in a large $V_d$.

A large $V_d$ may also result from sequestration into fat tissue, such as occurs with the antimalarial agent **chloroquine.**

### Drug Clearance

**Clearance (Cl)** is the most fundamental expression of drug elimination. It is defined as the volume of body fluid (blood) from which a drug is removed per unit of time. Although the clearance of a particular drug is **constant,** it is important to note that the amount of drug contained in the clearance volume will **vary** with the plasma drug concentration.

### Renal Clearance

Renal clearance can be calculated as the renal excretion rate divided by the plasma drug concentration (see Box 2.2). Drugs that are eliminated primarily by glomerular filtration, with little tubular secretion or reabsorption, will have a renal clearance approximately **equal to the creatinine clearance,** which is normally approximately 100 mL/min in an adult. A renal drug clearance higher than the creatinine clearance indicates that the drug is a substance that undergoes tubular secretion. A renal drug clearance lower than the creatinine clearance suggests that the drug is highly bound to plasma proteins or that it undergoes passive reabsorption from the renal tubules.

### Hepatic Clearance

Hepatic clearance is more difficult to determine than renal clearance. This is because hepatic drug elimination includes the biotransformation and biliary excretion of parent compounds. For this reason, hepatic clearance is usually determined by multiplying hepatic blood flow by the arteriovenous drug concentration difference.

## SINGLE-DOSE PHARMACOKINETICS

### First-Order Kinetics

Most drugs exhibit **first-order kinetics,** in which the rate of drug elimination (amount of drug eliminated per unit time) is proportional to the plasma drug concentration and follows an exponential decay function. Note that the rate of drug elimination is not the same as the elimination rate constant, $k_e$ (fraction of drug eliminated per unit time). A few drugs (e.g., ethanol) exhibit **zero-order kinetics,** in which the rate of drug elimination is constant and independent of plasma drug concentration (Fig. 2.8).

For drugs that exhibit first-order kinetics, the plasma drug concentration can be determined from the dose of a drug and its clearance. Because the plasma drug concentration is often correlated with the magnitude of a drug's effect, it is possible to use pharmacokinetic expressions to determine and adjust drug dosages to achieve a desired therapeutic effect (see Box 2.4).

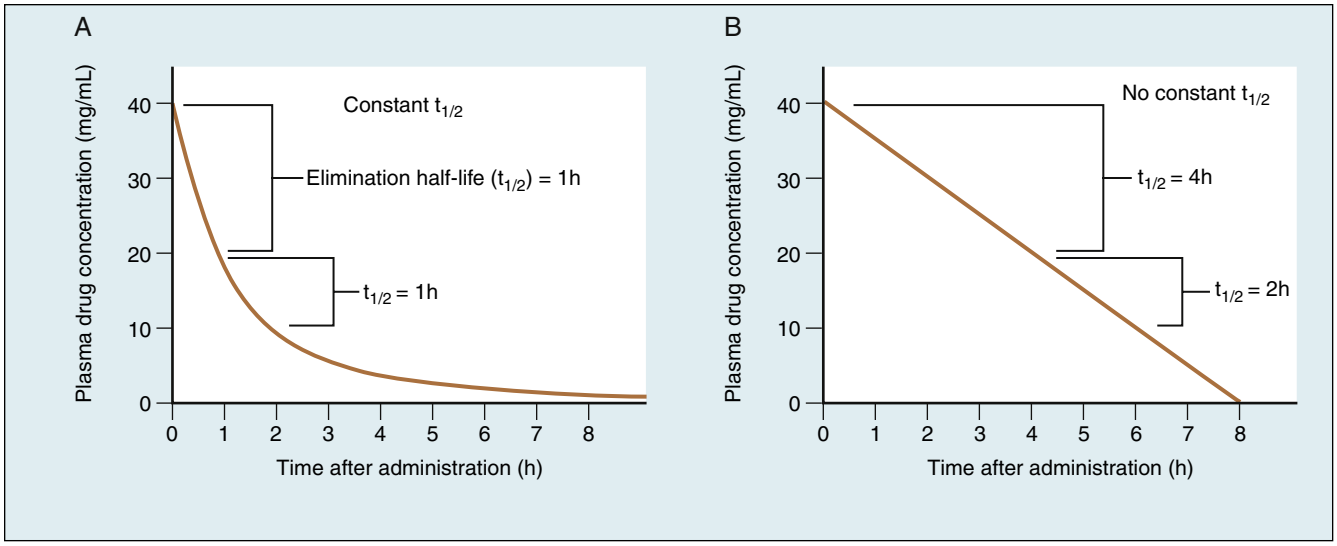



**FIG. 2.8** The kinetic order of drugs. In first-order kinetics (A) the rate of drug elimination is proportional to the plasma drug concentration. In zero-order kinetics (B) the rate of drug elimination is constant. The kinetic order of a drug is derived from the exponent *n* in the following expression:

$$\Delta[\text{Drug}]/\Delta t = -k_e\ [\text{Drug}]^n$$

where Δ represents change, [Drug] represents the plasma drug concentration, and t is time. If n is 1, then Δ[Drug]/ Δt is proportional to [Drug]. If n is 0, then Δ[Drug]/ Δt is constant ($k_e$), because $[\text{Drug}]^0$ equals 1.

The following principles pertain to first-order kinetics: A drug's **rate of elimination is equal to the plasma drug concentration multiplied by the drug clearance;** the elimination rate declines as the plasma concentration declines; and the half-life and clearance of the drug remain constant as long as renal and hepatic function do not change.

### Elimination Half-Life

Elimination half-life ($t_{½}$) is the time required to **reduce the plasma drug concentration by 50%.** It can be calculated from the elimination rate constant, but it is usually determined from the plasma drug concentration curve (Fig. 2.9). The half-life can also be expressed in terms of the drug's clearance and $V_d$, indicating that the drug's half-life will change when either of these factors is altered. The formula for relating half-life to clearance and $V_d$ is given in the legend of Fig. 2.9. Disease, age, and other physiologic variables can alter drug clearance or $V_d$ and thereby change the elimination half-life (see Chapter 4).

### Zero-Order Kinetics

The following principles pertain to zero-order kinetics: The rate of drug elimination is constant (see Fig. 2.8B); the drug's elimination half-life is **proportional** to the plasma drug concentration; the clearance is **inversely proportional** to the drug concentration; and a small increase in dosage can produce a disproportionate increase in the plasma drug concentration.

In many cases, the reason that the rate of drug elimination is constant is that the elimination process becomes **saturated.** This occurs, for example, at most plasma concentrations of **ethanol.** In some cases, drugs exhibit zero-order elimination when high doses are administered, which occurs, for example, with **aspirin** and the anticonvulsant **phenytoin** (DILANTIN) or when a hepatic or renal disease has impaired the drug elimination processes.

## CONTINUOUS-DOSE AND MULTIPLE-DOSE KINETICS

### Drug Accumulation and the Steady-State Principle

When a drug that exhibits first-order pharmacokinetics is administered to a patient continuously or intermittently, the drug will accumulate until it reaches a plateau or steady-state plasma drug concentration.

The basis for this accumulation to a steady state is shown in Fig. 2.10. When the drug is first administered, the rate of administration is much greater than the rate of elimination because the plasma concentration is so low. As the drug continues to be administered, the rate of drug elimination gradually increases, whereas the rate of administration remains constant. Eventually, as the plasma concentration rises sufficiently, the rate of drug elimination equals the rate of drug administration. At this point, the **steady-state equilibrium** is achieved.

### Time Required to Reach the Steady-State Condition

**Drug accumulation** to a steady state is a **first-order process** and therefore obeys the rule that half of the process is completed in a defined time. Because the time to reach the steady state is dependent on the time it takes for the rate of drug elimination to equal to the rate of drug administration, the time to reach the steady state is a function of the elimination half-life of the drug. Any first-order process requires approximately **five half-lives** to be completed; thus the time to reach the steady-state drug concentration is approximately five drug half-lives. If the half-life of a drug changes, then the time required to reach the steady state also changes. Note that the time required to reach the steady state is independent both of the drug dose and the rate or frequency of drug administration.

### Steady-State Drug Concentration

The steady-state drug concentration depends on the drug dose administered per unit of time and on the half-life of the

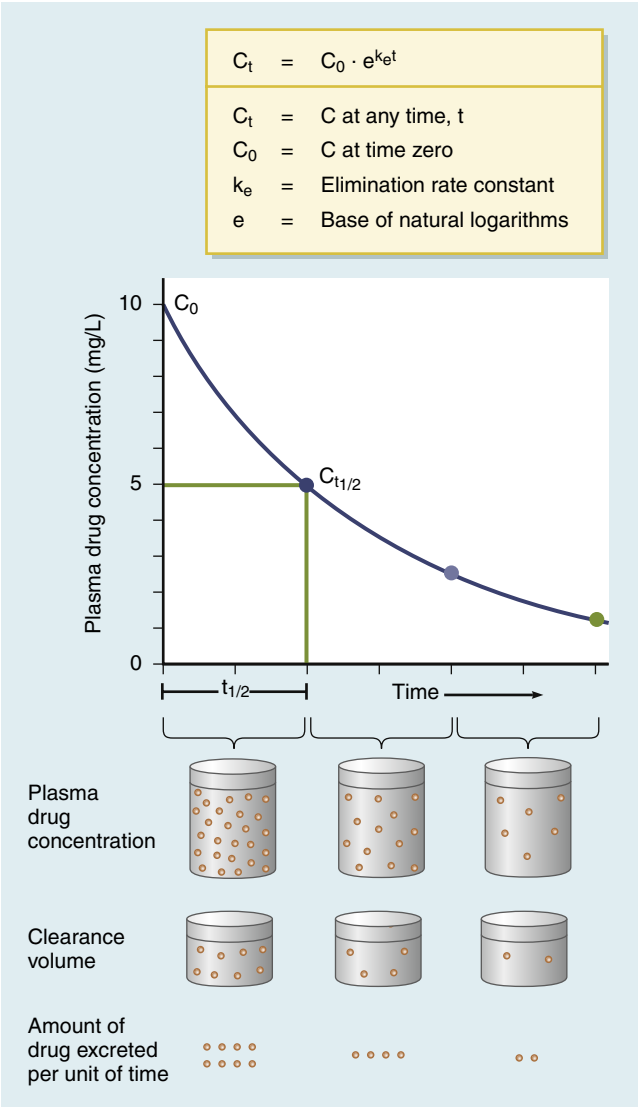



**Fig. 2.9** Drug half-life and clearance. The elimination half-life ($t_{½}$) is the time required to reduce the plasma drug concentration (C) by 50%. The formula is as follows:

$$t_{1/2} = 0.693 / k_e$$

where 0.693 is the natural logarithm of 2, and $k_e$ is the elimination rate constant. The half-life is often determined from the plasma drug concentration curve shown here. The clearance (Cl) is the volume of fluid from which a drug is eliminated per unit of time. It can be calculated as the product of the volume of distribution, $V_d$, and $k_e$. If $0.693/t_{½}$ is substituted for $k_e$, the equation is as follows:

$$Cl = 0.693 V_d / t_{1/2}$$

Thus a drug's clearance is directly proportional to its volume of distribution and is inversely proportional to its half-life.

drug. Fig. 2.11 illustrates typical plasma concentration curves after drugs are **administered continuously** or **intermittently.** If the dose is doubled, the steady-state concentration is also doubled (Fig. 2.11A). Likewise, if the half-life is doubled, the steady-state concentration is doubled (Fig. 2.11B).

A drug administered intermittently will **accumulate to a steady state at the same rate** as a drug given by continuous infusion, but the plasma drug concentration will fluctuate as each dose is absorbed and eliminated. The average steady-state plasma drug concentration with intermittent intravenous administration will be the same as if the equivalent dose were administered by continuous infusion (Fig. 2.11C). A comparison of the steady-state drug levels following continuous intravenous infusion, multiple oral doses, and a single oral dose is shown in Fig. 2.11D. With intermittent oral administration, the bioavailability of the drug will also influence the steady-state plasma concentration.

## Dosage Calculations

The methods for calculating both the loading dose and the maintenance dose are given in Box 2.4.

### Loading Dose

**A loading dose,** or **priming dose,** is given to rapidly establish a therapeutic plasma drug concentration. The loading dose can be calculated by multiplying the $V_d$ by the desired plasma drug concentration. The loading dose, which is larger than the maintenance dose, is generally administered

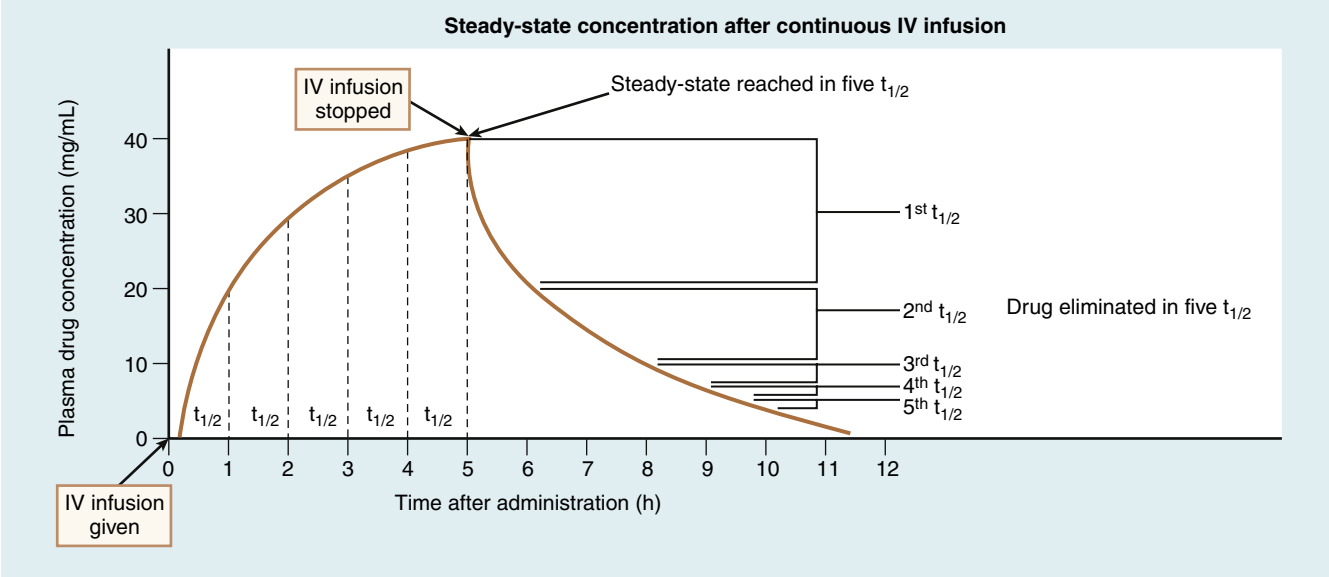



**Fig. 2.10** Drug accumulation to the steady state. The time required to reach the steady state depends on the half-life ($t_{½}$); it does not depend on the dose or dosage interval. The steady-state drug concentration depends on the drug dose administered per unit of time and on the drug's clearance or $t_{½}$.

as a single dose, but it can be divided into fractions that are given over several hours. A **divided loading dose** is sometimes used for drugs that are more toxic (e.g., **digitalis glycosides** used to treat congestive heart failure).

### Maintenance Dose

A **maintenance dose** is given to establish or maintain the **desired steady-state** plasma drug concentration. For drugs given intermittently, the maintenance dose is one of a series of doses administered at regular intervals. The amount of drug to be given is based on the principle that, at the steady state, the rate of drug administration equals the rate of drug elimination. To determine the rate of drug elimination, the drug clearance is multiplied by the average steady-state plasma drug concentration. The maintenance dose is then calculated as the rate of drug elimination multiplied by the dosage intervals. If the drug is administered orally, its bioavailability must also be included in the equation.

## SUMMARY OF IMPORTANT POINTS

- Most drugs are absorbed by passive diffusion across cell membranes or between cells. The rate of passive diffusion of a drug across cell membranes is proportional to the drug's lipid solubility and the surface area available for absorption. Only the nonionized form of weak acids and bases is lipid soluble.
- The ratio of the ionized form to the nonionized form of a weak acid or base can be determined from the $pK_a$ of the drug and the pH of the body fluid in which the drug is dissolved.
- The distribution of a drug is influenced by organ blood flow and by the plasma protein binding, molecular size, and lipid solubility of the drug. Only drugs with high lipid solubility can penetrate the blood-brain barrier.
- The volume of distribution is the volume of fluid in which a drug would need to be dissolved to have the same concentration in that volume as it does in plasma. It is calculated by dividing the drug dose by the plasma drug concentration at time zero.
- Many drugs are metabolized (biotransformed) before excretion. Drug metabolites can be pharmacologically active or inactive. Phase I reactions include oxidative, reductive, and hydrolytic reactions, whereas phase II reactions conjugate a drug with an endogenous substance. The CYP enzymes located in the endoplasmic reticulum of liver cells are the most important oxidative metabolic enzymes.
- Most drugs are excreted in the urine, either as the parent compound and/or as drug metabolites, and undergo the processes of glomerular filtration, active tubular secretion, and passive tubular reabsorption. The renal clearance of a drug can be calculated by dividing the renal excretion rate by the plasma drug concentration.
- Most drugs exhibit first-order kinetics, in which the rate of drug elimination is proportional to the plasma drug concentration at any given time. If drug elimination mechanisms (biotransformation and excretion) become saturated, a drug can exhibit zero-order kinetics, in which the rate of drug elimination is constant.
- In first-order kinetics, a drug's half-life and clearance are constant as long as elimination processes are constant. The half-life is the time required for the plasma drug concentration to decrease by 50%. The clearance is the volume of plasma from which a drug is eliminated per unit of time.
- The oral bioavailability of a drug is the fraction of the administered dose that reaches the bloodstream in an active form. It is determined by dividing the AUC after oral administration by the AUC after intravenous administration. Factors that reduce bioavailability include incomplete tablet disintegration and first-pass and gastric inactivation of a drug.
- With continuous or intermittent drug administration, the plasma drug concentration increases until it reaches a steady-state condition, in which the rate of

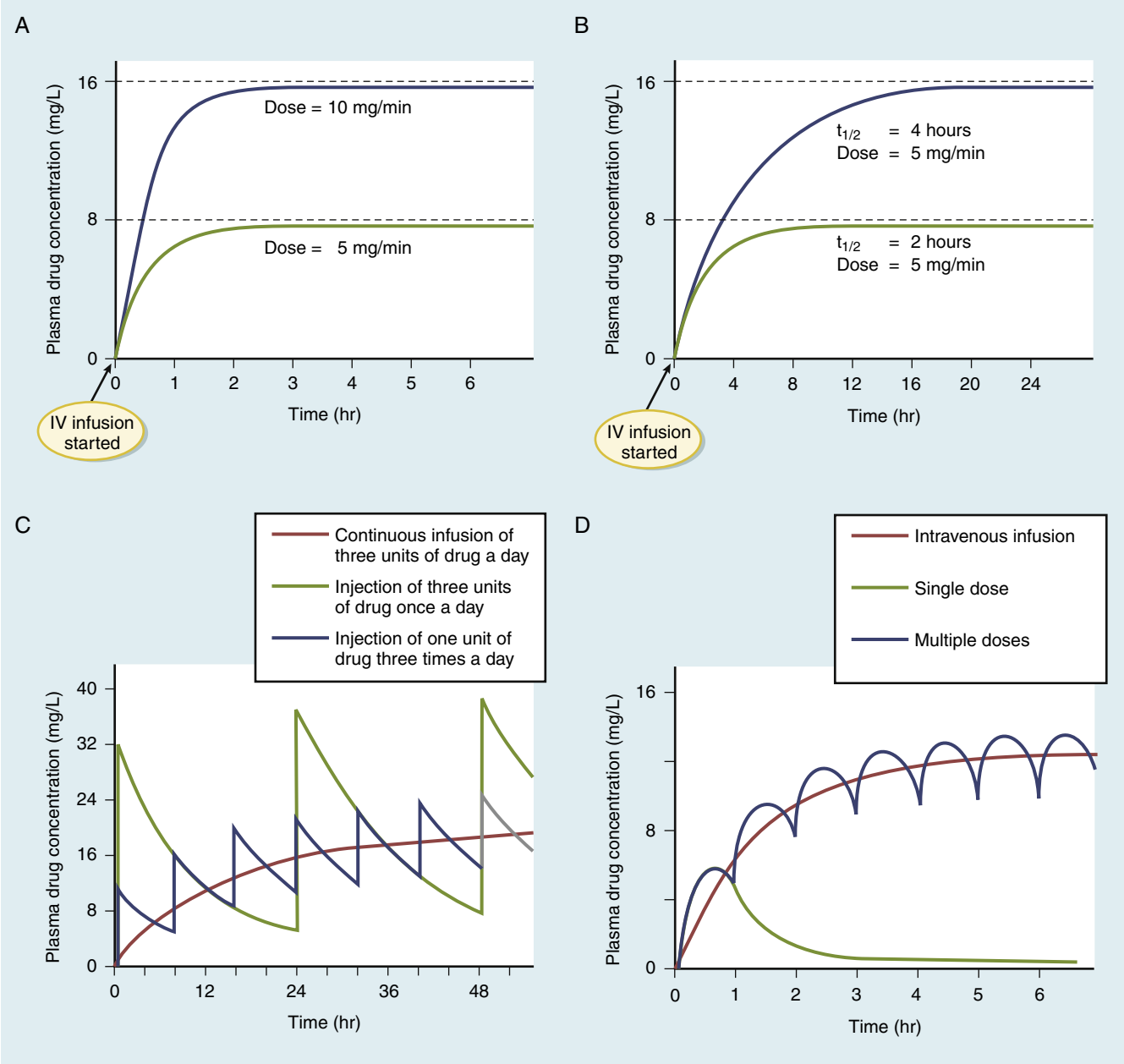



**Fig. 2.11** Plasma drug concentrations after continuous or intermittent drug administration. (A) The steady-state plasma drug concentration is proportional to the dose administered per unit of time. (B) The steady-state plasma drug concentration is directly proportional to the half-life (and is inversely related to clearance). (C) The average steady-state concentration is the same for intermittent infusion as it is for continuous infusion. However, with intermittent drug administration, the plasma concentrations fluctuate between doses, and the size of fluctuations increases as the dosage interval increases. (D) Plasma drug concentrations after intermittent oral administration are affected by the rates of drug absorption, distribution, and elimination. If only one dose is given, the peak in plasma drug concentration is followed by a continuous decline in the curve.

drug elimination is equal to the rate of drug administration. It takes approximately four to five drug half-lives to achieve the steady-state condition.

- The steady-state drug concentration can be calculated as the dose per unit of time divided by the clearance, and this equation can be rearranged to determine the dose per unit of time required to establish a specified steady-state drug concentration.
- A loading dose is a single or divided dose given to rapidly establish a therapeutic plasma drug concentration. The dose can be calculated by multiplying the volume of distribution by the desired plasma drug concentration.

## Review Questions

1. If food decreases the rate but not the extent of the absorption of a particular drug from the gastrointestinal tract, then taking the drug with food will result in a smaller
   (A) area under the plasma drug concentration time curve.
   (B) maximal plasma drug concentration.
   (C) time at which the maximal plasma drug concentration occurs.
   (D) fractional bioavailability.
   (E) total clearance.

2. If a drug exhibits first-order elimination, then
   (A) the elimination half-life is proportional to the plasma drug concentration.
   (B) the drug is eliminated at a constant rate.
   (C) hepatic drug metabolizing enzymes are saturated.
   (D) drug clearance will increase if the plasma drug concentration increases.
   (E) the rate of drug elimination (mg/min) is proportional to the plasma drug concentration.
3. After a person ingests an overdose of an opioid analgesic, the plasma drug concentration is found to be 32 mg/L. How long will it take to reach a safe plasma concentration of 2 mg/L if the drug's half-life is 6 hours?
   (A) 12 hours
   (B) 24 hours
   (C) 48 hours
   (D) 72 hours
   (E) 1 week
4. What dose of a drug should be injected intravenously every 8 hours to obtain an average steady-state plasma drug concentration of 5 mg/L if the drug's volume of distribution is 30 L and its clearance is 8 L/h?
   (A) 40 mg
   (B) 80 mg
   (C) 160 mg
   (D) 320 mg
   (E) 400 mg
5. The volume of distribution of a drug will be greater if the drug
   (A) is more ionized inside cells than in plasma.
   (B) is administered very rapidly.
   (C) is highly ionized in plasma.
   (D) has poor lipid solubility.
   (E) has a high molecular weight.