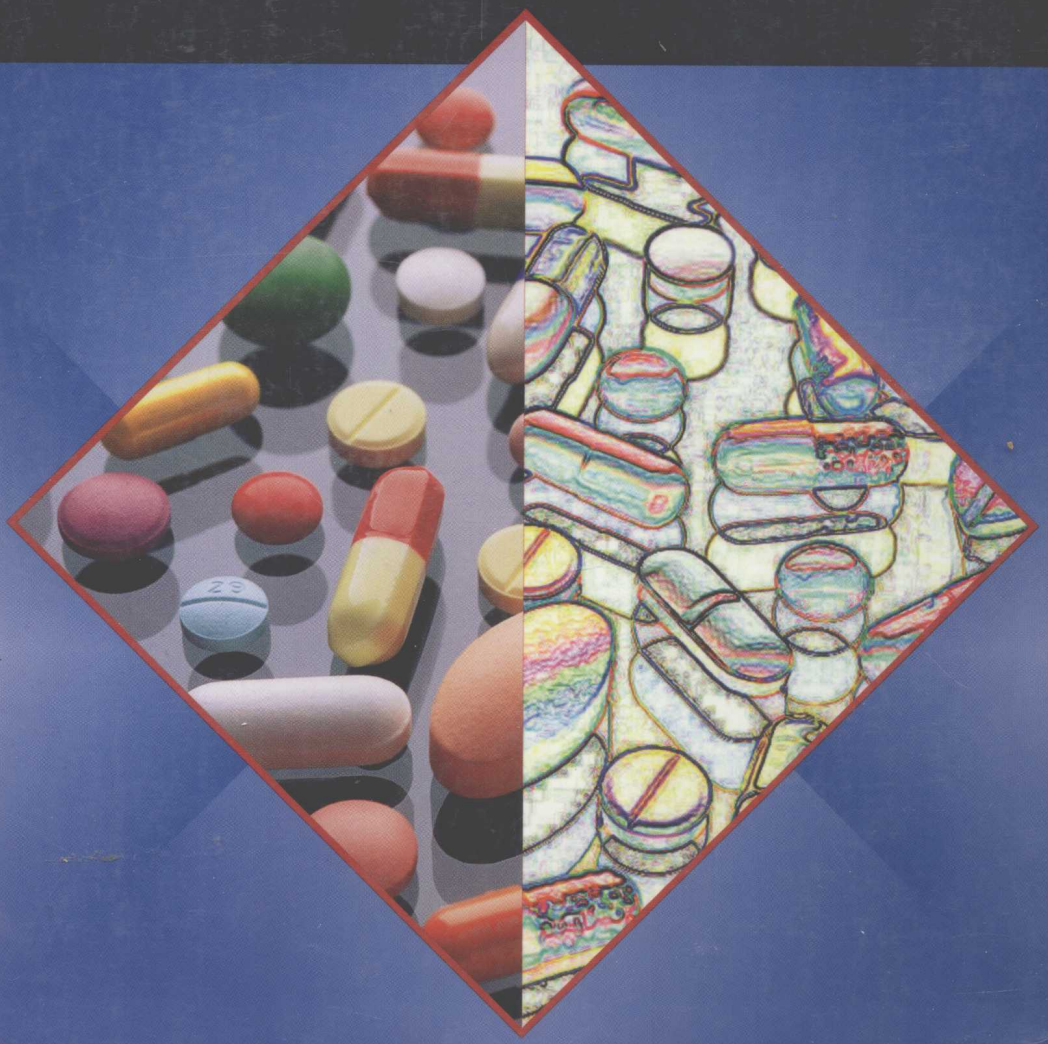
Pharmacology

A 2-in-1 Reference for Nurses



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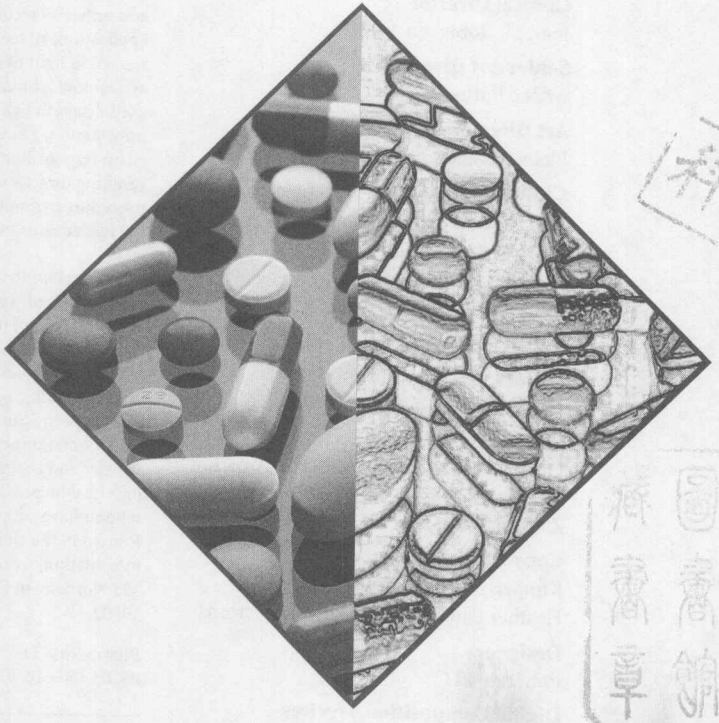

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A **Wolters Kluwer** Company
Philadelphia • Baltimore • New York • London
Buenos Aires • Hong Kong • Sydney • Tokyo

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Pharm2in1- D
06 05 04 10 9 8 7 6 5 4 3 2

Library of Congress Cataloging-in Publication Data

Pharmacology: a 2-in-1 reference for nurses.
p. ; cm.
Includes index.
1. Pharmacology 2. Nursing. I. Lippincott Williams & Wilkins.
[DNLM: 1. Pharmacology—methods—Nurses' Instruction. 2. Drug Therapy—nursing. 3. Pharmaceutical Preparations—administration & dosage. QV 4 P53608 2004]
RM300.P5175 2004
615'.1—dc22
ISBN 1-58255-320-3 (alk. paper) 2003027064

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Foreword

Take a moment to consider these questions. How much can you call to mind about drugs in general, why drugs of a certain class act the way they do, which related drugs might cause similar interactions or adverse effects, and which assessment, monitoring, and follow-up steps you should pursue if your patient's regimen includes less-familiar drugs?

The demands and hectic pace of everyday practice requires you to work efficiently; time management is essential. That's why I'm pleased to recommend *Pharmacology: A 2-in-1 Reference for Nurses.* Whether you need a minor memory booster or a complete refresher course, this book has it.

Ingenious format

The first thing you'll notice about *Pharmacology: A 2-in-1 Reference for Nurses* is its ingenious two-column format. The inner two-thirds of each page contains a full narrative on drugs and their classes. The outer third of each page contains abbreviated, bulleted information that's perfect for quick scanning. The full effect of this two-part design is that you can skip the information you already know, quickly review anything you want to clarify or update, and easily go in-depth whenever you choose—all in the same book, often on the same page.

For example, if you're pressed for time or you just want a quick refresher, skim the narrow column on the outside edge of each page. Here you'll find all the most pertinent points of each drug class and many individual drugs in convenient bulleted form. If you want a more extensive review, simply shift your eyes over to the main column, where you'll find a more expanded version of the same topic. The information is still concise and clear, just more detailed.

Practical approach

And here's an important distinction. It isn't just the flexible format that sets this book apart. It's the content itself.

For one thing, it's grouped in the most practical way possible: by therapeutic use. You'll find individual chapters on the most important drug groups, such as cardiovascular drugs, respiratory drugs, GI drugs, anti-infectives, antineoplastics, neurologic drugs, and much more. You'll also find full chapters on drug classes of increasing scope and importance, such as immunomodulating drugs, psychotropic drugs, and endocrine drugs.

For another thing, drug information is organized to follow a consistent, practical order: pharmacokinetics, pharmacodynamics, pharmacotherapeutics, interactions, adverse reactions, and nursing considerations.

You'll also find chapters on equally practical matters, such as essential dosage calculations, step-by-step drug administration techniques, best drug-error sidesteps, and the must-know pharmacologic fundamentals.

A final practical aspect of this flexible book is its special logo features. These targeted short pieces call your attention to selected major topics and offer concise, scan-and-go information. Look for these helpful boxes and illustrations throughout the text:

✦ *Eye on drug action:* Illustrations to help you visualize—and remember—the often complicated ways drugs work.

✦ *Lifespan:* Considerations to carefully care for pregnant, breast-feeding, pediatric, or geriatric patients.

✦ *Warning:* Highlighted information about dangerous, hazardous, or life-threatening developments and how to avoid them.

✦ *Anatomy & physiology:* Illustrations of body systems and functions to refresh your memory.

✦ *Patient teaching:* Important points to tell patients about a drug class or a particular drug.

✦ *Clinical alert:* A colored logo to draw your attention to vitally important information in the main body of the text.

Every nurse knows that a sound understanding of pharmacology goes hand in hand with safe drug administration. *Pharmacology: A 2-in-1 Reference for Nurses* gives you as quick a review as you want and as complete a reference as you need, all in a surprisingly practical package. I recommend it enthusiastically.

Lisa A. Salamon, RNC, MSN, CNS, ETN
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Contents

1

Fundamentals of clinical pharmacology

Before you can calculate dosages and give drugs safely, you need to understand the fundamental principles of pharmacology. Besides being aware of how drugs are named and made, you need to know their pharmacokinetics, pharmacodynamics, and pharmacotherapeutics, which include drug interactions and adverse reactions. You also need to consider the unique needs of pregnant, breast-feeding, pediatric, and geriatric patients.

Drug names and classes

Nearly every drug has three different names. Its *chemical* name is the scientific name that precisely describes its atomic and molecular structure. Its *generic,* or *nonproprietary,* name typically is an abbreviation of its chemical name. Its *trade* name, which is also called the *brand* or *proprietary* name, is selected by the drug manufacturer. Trade names are protected by copyright.

To avoid confusion, refer to a drug by its generic name because any drug can have many trade names. For example, use the generic name diltiazem when discussing this drug, instead of Cardizem, Tiazac, or any of its other trade names.

Every drug also belongs to at least two classes: a pharmacologic class and a therapeutic class. Drugs with similar chemical characteristics, such as beta blockers, fall into the same pharmacologic class. Drugs used to treat the same disorder fall into the same therapeutic class. For example, all drugs used to treat hypertension are part of the antihypertensive therapeutic class, even if they belong to different pharmacologic classes.

The three names of most drugs

- Chemical
- Generic
- Trade

The two classes of every drug

- Pharmacologic
- Therapeutic

Drug sources

Traditionally, drugs were derived from natural sources, such as plants, animals, and minerals. Today, most drugs are produced in laboratories and can be natural, synthetic, or a combination of the two.

Plants

The earliest drugs used all parts of the plants, including the leaves, roots, bulb, stem, seeds, buds, and blossoms. Because of this, harmful substances commonly found their way into the mixture.

Active components of plants

- Alkaloids
- Glycosides
- Gums
- Resins
- Oils

As the understanding of plants as drug sources became more sophisticated, researchers tried to isolate and intensify active components while avoiding harmful ones. Several types of active components vary in their character and effects.

- *Alkaloids,* the most active component in plants, react with acids to form a salt that dissolves readily in body fluids. The names of alkaloids and their salts usually end in *–ine,* such as atropine, caffeine, and nicotine.
- *Glycosides* also appear in plants. Their names usually end in *–in* like digoxin.
- *Gums,* usually in the form of polysaccharides, produce viscous solutions and allow products to attract and hold water. An example is psyllium, which is found in over-the-counter (OTC) laxatives. The laxative effect is probably due to the swelling of the psyllium as it absorbs water. This absorption increases stool bulk and stimulates peristalsis.
- *Resins,* primarily from pine tree sap, can be used for their actions as local irritants, laxatives, and caustic agents.
- *Oils,* which are thick and sometimes greasy liquids, may be volatile or fixed. Volatile oils, which evaporate easily, include peppermint, spearmint, and juniper. Fixed oils, including the laxative castor oil, don't evaporate easily.

Animals

Body fluids and glands of animals also can serve as drug sources. Drugs obtained from animal sources include:

Drugs from animal sources

- Hormones
- Oils
- Fats
- Enzymes
- Vaccines

- *hormones* such as insulin
- *oils* and *fats* such as cod-liver oil
- *enzymes,* which are produced by living cells and act as catalysts, such as pancreatin and pepsin
- *vaccines,* which are suspensions of killed, modified, or attenuated microorganisms.

Minerals

Metallic and nonmetallic minerals provide inorganic material that isn't available from plants or animals. Minerals may be used as they occur in nature or may be combined with other ingredients. Some drugs that contain minerals are iodine and epsom salts.

Synthetic drugs

Today, researchers blend traditional knowledge with modern chemistry to develop synthetic drugs. One advantage of synthetic drugs is that they're free from the impurities found in natural substances.

Advantages of synthetic drugs

- They're free from impurities found in natural substances
- Their molecular structure can be manipulated

Another advantage is that drug developers can manipulate a drug's molecular structure slightly to make it more effective. Researchers commonly do this with antibiotics to make them effective against different organisms. For example, an organism cultured in seawater produced first-generation cephalosporins, which were effective against *Streptococcus, Staphylococcus, Escherichia coli, Proteus mirabilis,* and *Shigella*. Changes to the drugs' chemical structure resulted in second-generation cephalosporins, which effectively treated infections caused by *Bacteroides fragilis* and *Haemophilus influenzae*, and then in third-generation drugs, which were effective against *Pseudomonas*. Over time, bacteria developed resistance to those drugs, which prompted the development of fourth-generation cephalosporins. These

Phases of new drug development

Before the Food and Drug Administration (FDA) approves the application for a new drug, the drug undergoes clinical evaluation divided into three phases. The fourth phase isn't required for approval but is often done to make sure the drug is working properly in a clinical setting.

Phase I: The drug is tested on healthy volunteers.
Phase II: The drug is tested on people who have the disease for which the drug is thought to be effective.
Phase III: The drug is given to large numbers of patients in medical research centers. This larger sampling provides information about infrequent or rare adverse reactions. If phase III studies are satisfactory, the FDA approves the new drug application.
Phase IV: This voluntary phase involves postmarket surveillance of the drug's therapeutic effects. The pharmaceutical company receives reports from prescribers about the drug's therapeutic and adverse effects. Drugs that are found to be toxic are removed from the market.

drugs, which are active against a broad spectrum of gram-negative and gram-positive organisms, are powerful tools for fighting serious, life-threatening infections.

Recombinant deoxyribonucleic acid (DNA) research has led to the combination of natural and synthetic sources of drugs. For example, by reordering genetic information, scientists have developed bacteria that produce insulin.

NEW DRUG DEVELOPMENT

In the past, drugs were found by trial and error. Now, they're developed primarily by systematic scientific research. The Food and Drug Administration (FDA) carefully monitors new drug development, which can take many years.

First, the FDA reviews extensive animal studies and data on the safety and effectiveness of the proposed drug. Then it approves an application for an investigational new drug (IND). Next, the drug goes through four phases of clinical testing in humans to obtain information on its purity, bioavailability, potency, efficacy, safety, and toxicity. Depending on the test results, the studies can be stopped at any phase. (See *Phases of new drug development.*)

The three types of INDs are an Investigator IND, an Emergency Use IND, and a Treatment IND.

✦ An *Investigator IND* is submitted by the physician who initiates and conducts the investigation. The investigational drug must be administered or dispensed under his immediate direction. The study may involve an unapproved drug or an approved drug that's being tested for use in a new indication or patient population.

✦ An *Emergency Use IND* authorizes the use of an experimental drug in emergencies when time doesn't allow for IND submission according to established guidelines. It also may be used when patients don't meet the criteria of an existing study protocol or when an approved study protocol doesn't exist.

✦ A *Treatment IND* applies to an experimental drug that shows promise in clinical testing and is desperately needed to treat a serious or immediately life-threatening illness. This IND can be used while researchers complete the final clinical work and the FDA reviews the data.

Sponsors of drugs that reach phase II or III clinical trials can apply for FDA approval of Treatment IND status. When the IND is approved, the sponsor supplies the drug to prescribers whose patients meet appropriate criteria.

Three types of investigational new drugs

✦ Investigator IND
✦ Emergency Use IND
✦ Treatment IND

LABELED AND UNLABELED USES

When approving a new drug, the FDA accepts it only for the indications for which phase II and III clinical studies have shown it to be safe and effective. These indications are approved, or labeled; all others are unapproved, or unlabeled.

Difference between labeled and unlabeled uses

- Labeled uses are FDA-approved indications for which phase II and III clinical studies have shown safety and effectiveness.
- Unlabeled uses are indications that aren't FDA-approved but that the drug effectively treats in clinical use.

For example, the FDA may approve a new drug to treat hypertension if phase II and III studies show that it's safe and effective in patients with hypertension. If the drug also works well as an antianginal, the FDA can't approve it for this indication unless formal studies in patients with angina pectoris are completed successfully. Such a drug is unapproved for treatment of angina pectoris, yet it may be used for this unlabeled indication, based on empirical evidence.

Here's how a drug can start being used for an unlabeled indication. After ordering a new drug approved to treat hypertension, a prescriber may discover that it also decreases the patient's angina. The prescriber may share this finding with colleagues in medical journals or at meetings, and they may prescribe it for unlabeled uses, too.

The FDA recognizes that a drug's labeling doesn't always contain the most current information about its use. Therefore, after the FDA approves a drug for one indication, a prescriber legally may order it, a pharmacist may dispense it, and a nurse may give it to a patient for any labeled — or unlabeled — indication.

Although prescribers may prescribe, dispense, and give a drug for an unlabeled use, the FDA forbids the manufacturer from promoting a drug for any unlabeled indications. That's why drug package inserts and the *Physicians' Desk Reference* contain no information about unlabeled uses and why pharmaceutical sales representatives can't discuss such uses.

Many drugs are commonly prescribed for unlabeled uses, which later become approved uses. Tretinoin (Retin-A) is an example. Once only prescribed for acne, it was noted to help eliminate wrinkles. Thus, the drug was prescribed for wrinkles. Although tretinoin now has FDA approval for this use, it continues to have off-label uses for certain skin cancers and dermatologic conditions.

PHARMACOKINETICS

What is pharmacokinetics?

- A drug's actions as it moves through the body

Kinetics refers to movement. Pharmacokinetics refers to a drug's actions as it moves through the body. Specifically, pharmacokinetics describes how a drug is absorbed into, distributed through, metabolized within, and excreted from the body. This branch of pharmacology also reflects the drug's onset of action, peak level, and duration of action.

ABSORPTION

Drug absorption covers a drug's progress from the time it's given, through the time it moves into tissues, until it becomes available for use by the body. At the cellular level, drug absorption depends primarily on transport mechanisms.

Transport mechanisms

The two types of transport mechanisms

- In passive transport, a drug moves from an area of higher concentration to one of lower concentration, which requires no cellular energy.
- In active transport, a drug moves from an area of lower concentration to one of higher concentration, which requires cellular energy.

Two mechanisms are responsible for the absorption of most drugs: passive and active transport. Passive transport requires no cellular energy because the drug moves from an area of higher concentration to one of lower concentration. It occurs when small molecules diffuse across membranes. Diffusion is complete when the drug concentration on both sides of the membrane is equal.

Active transport requires cellular energy to move the drug from an area of lower concentration to one of higher concentration. Active transport is used to absorb electrolytes, such as sodium and potassium, as well as some drugs, such as levodopa.

Pinocytosis is a unique form of active transport that happens when a cell engulfs a drug particle. During pinocytosis, the drug doesn't need to be dissolved because the cell forms a vesicle for drug transport across the cell membrane and into the inner cell. Pinocytosis commonly occurs to transport fat-soluble vitamins, such as vitamins A, D, E, and K.

What affects absorption

The administration route plays a key role in absorption. When only a few cells separate the drug from systemic circulation, absorption takes place rapidly and the drug quickly reaches a therapeutic level in the body. Typically, absorption occurs within seconds or minutes when a drug is given by the sublingual, I.V., or inhalation route.

Absorption occurs more slowly when a drug is given by the oral, I.M., or subcutaneous (S.C.) route because the complex membranes of GI mucosa, muscles, and skin delay drug passage. With rectal or sustained-release drugs, absorption occurs even more slowly, taking several hours or days to reach a peak level.

Other factors can affect the rate of drug absorption. First, most oral drug absorption takes place in the small intestine. If a large portion of a patient's small intestine has been surgically removed, drug absorption decreases because of the reduced surface area and intestinal transit time.

Second, a drug absorbed by the small intestine travels to the liver before circulating to the rest of the body. The liver can perform a first-pass effect, metabolizing much of the drug to an inactive form before it enters the circulation and reaches its site of action. If the first-pass effect significantly reduces the amount of active drug released into the systemic circulation, the patient will need a higher drug dosage to obtain the desired effect. This explains why a drug's oral dose may be much higher than its I.V. dose for the same indication.

Third, increased blood flow to an absorption site improves drug absorption and leads to a quicker onset of drug action. Conversely, reduced blood flow decreases absorption and leads to a more gradual onset. For faster absorption of an I.M. drug, for example, the deltoid muscle is a good choice because blood flows faster through the deltoid muscle than through the gluteal muscle. The gluteal muscle, however, can accommodate a larger volume of drug than the deltoid muscle.

Fourth, pain and stress can decrease the amount of drug absorbed. This effect may result from altered blood flow, reduced GI motility, or gastric retention triggered by the autonomic nervous system's response to pain.

Fifth, high-fat meals and solid foods slow the rate at which the contents of the stomach enter the intestines. This, in turn, delays intestinal absorption of a drug.

Sixth, the drug formulation (such as tablets, capsules, liquids, sustained-release forms, inactive ingredients, and coatings) affects the drug absorption rate and the time needed to reach a peak level.

Finally, combining one drug with another or with food or an herbal preparation can cause interactions that increase or decrease drug absorption.

Factors affecting drug absorption

- Administration route
- Intestinal surface area and transit time
- First-pass effect
- Blood flow to the absorption site
- Pain and stress
- GI motility
- Drug formulation
- Interactions with other drugs, food, or herbs
- High-fat and solid food

DISTRIBUTION

Drug distribution is the process by which a drug is delivered to body tissues and fluids. After a drug is absorbed, its distribution is influenced by blood flow, its solubility and ability to bind with proteins, and the volume of distribution.

What is distribution?

- Process that allows drug delivery to tissues and fluid

Factors affecting drug distribution

- Blood flow
- Drug solubility
- Protein-binding capability
- Volume of distribution

Blood flow and drug solubility

Once a drug reaches the bloodstream, its distribution depends on blood flow. A drug is distributed rapidly to organs with a large blood supply, such as the heart, liver, and kidneys. It's distributed more gradually to other internal organs, skin, fat, and muscle.

Solubility also helps determine distribution. A drug's ability to cross a cell membrane depends on whether it's soluble in fats (lipids) or water. A lipid-soluble drug easily crosses cell membranes, whereas a water-soluble drug doesn't.

Protein binding

The degree of protein binding influences the distribution and storage of a drug. When distributed in the vascular or lymphatic system, a drug comes in contact with proteins. There, it remains free (unbound) or it binds to a plasma carrier protein, storage tissue protein, or receptor protein. As soon as a drug binds to a plasma carrier protein or storage tissue protein, it becomes inactive, which means it can't bind to a receptor protein or exert any therapeutic activity. However, a bound drug can free itself rapidly to maintain a balance between the amounts of free and bound drug. Only the free drug remains active.

The percentage of drug that remains free and available for activity depends on the amount of protein available for binding. The major source for carrier protein binding is plasma albumin.

The percentage of free drug differs widely among drugs. For example, a highly protein-bound drug, such as warfarin, is more than 80% bound to protein. A poorly protein-bound drug, such as cimetidine, may be less than 20% bound to protein.

The amount of free drug in the plasma also differs among patients, depending on their health status. For example, a patient with malnutrition typically has less protein and plasma albumin in his body. His decreased plasma albumin level — and number of protein-binding sites — can boost the amount of free drug in his plasma, which may be undesirable. That's why you should note changes in the patient's health status that could alter the percentage of free drug in his plasma.

Low-volume distribution

- Is caused by high water solubility
- Is caused by high protein-binding
- Results in a higher drug level

Volume of distribution

Volume of distribution isn't actual volume, but a measure of the size of a compartment, such as blood, total body water, or fat, that would be filled by the amount of drug in the same concentration as that found in the blood or plasma. Keep in mind, however, that a drug's volume of distribution is unrelated to its effectiveness or duration of action.

A highly water-soluble drug possesses a small volume of distribution and has a high blood concentration level. In contrast, a highly lipid-soluble drug possesses a large volume of distribution and has a low blood concentration level. Factors that tend to keep a drug in circulation, such as high water solubility and high protein binding, result in a lower volume of distribution and a higher level. Conversely, factors that promote drug movement from the blood to other compartments, such as high lipid solubility (promoting storage of the drug in fat) and high tissue binding, result in a higher volume of distribution and a lower blood concentration level.

High-volume distribution

- Is caused by high lipid solubility
- Is caused by high tissue-binding
- Results in a lower drug level

A drug's ability to cross barriers, such as the blood-brain barrier, can influence a drug's volume of distribution. The blood-brain barrier refers to a network of capillary endothelial cells in the brain. These cells have no pores and are surrounded by a sheath of glial connective tissue that makes them impermeable to water-soluble drugs. The network excludes most ionized drug molecules, such as dopamine, from the brain. However, it allows nonionized, unbound drug molecules, such as barbiturates, to pass readily and enter the brain.

Don't assume that a drug is well distributed throughout the body. Abscesses, exudates, glands, and tumors can adversely affect drug distribution. Also, variable drug concentrations among different organs and tissues within a single organ can complicate drug distribution. The differences in drug levels in tissues result from such factors as a tissue's affinity for the drug, blood flow, and protein-binding sites.

Metabolism

Drug metabolism, or biotransformation, refers to the body's ability to change a drug from its original form to a more or less active form that can then be excreted. Through metabolism, the body detoxifies and disposes of foreign substances such as drugs. In most cases, enzymes increase the drug's water solubility so that the kidneys can excrete the drug. For some drugs, enzymes may alter their lipid solubility so that the end products enter into and are excreted in bile. Using the kidneys or biliary system for disposal, the body usually transforms the drug into a readily eliminated, pharmacologically inactive substance. Usually, the resulting product, called a metabolite, is an inactive form of the original drug. For some drugs, however, one or all of the metabolites may have some drug activity. These are called active metabolites. All metabolites, active or inactive, may undergo further metabolism or may be excreted from the body unchanged.

Some drugs are given as prodrugs (inactive drugs that don't become active until they're metabolized). After oral administration, intestinal and hepatic enzymes rapidly convert this type of drug to its active form. For example, the prodrug valganciclovir is metabolized into the active drug ganciclovir.

What affects metabolism

Not all drugs are metabolized to the same extent or by the same mechanisms. Some drugs, such as aminoglycosides, aren't metabolized; they pass through the body and are excreted unchanged. Other drugs, such as barbiturates, stimulate or induce enzyme metabolic activity, thus reducing the amount of active drug in the body.

In contrast, some drugs inhibit or compete for enzyme metabolism, which may cause other drugs to accumulate. Accumulation increases the risk of adverse reactions and drug toxicity. Before interpreting a drug response or adjusting therapy because of an inappropriate level of an active drug, check for drug-induced changes in drug metabolism.

Disease-induced changes can interfere with drug metabolism. When end-stage cirrhosis damages the liver enough to reduce liver blood flow, the supply of a drug to liver enzyme metabolic sites decreases. When heart failure decreases cardiac output, drug metabolism decreases because the drug delivery to liver metabolic sites becomes inefficient. Genetics also may play a part in drug metabolism. Certain ethnic groups are slow or fast acetylators, which refers to their rate of sulfamethazine acetylation (a common metabolic process) for such drugs as isoniazid, hydralazine, and many sulfa drugs. Slow acetylators may be at increased risk for toxicity because of increased exposure to a drug. Fast acetylators may metabolize a drug too rapidly, minimizing its therapeutic effects. (See *Predicting the effects of genetics on drug metabolism*, page 8.)

Developmental changes also can affect drug metabolism. For instance, infants have immature livers that reduce the rate of metabolism. Geriatric patients experience a decline in liver size, blood flow, and enzyme production that also slows metabolism.

What is metabolism?

- Alters a drug to a more active or less active form
- Helps convert the drug to a more water soluble form, facilitating excretion

Factors affecting metabolism

- Drugs that induce enzyme activity
- Drugs that inhibit enzyme activity
- Disease, such as cirrhosis and heart failure
- Genetics
- Age-related differences

Ways to evaluate drug acetylation

- Check the patient's ethnicity.
- Monitor the drug level.
- Assess for therapeutic and adverse drug effects.

Predicting the effects of genetics on drug metabolism

Certain percentages of different ethnic groups may be slow acetylators. The table below can help you predict which patients may have this altered metabolism. However, the only way to determine a patient's acetylation rate is to monitor the drug level in his blood and to assess him for therapeutic and adverse effects.

ETHNIC GROUP	PERCENTAGE OF SLOW ACETYLATORS	ETHNIC GROUP	PERCENTAGE OF SLOW ACETYLATORS
Black	40% to 70%	**Indian**	60%
Canadian Indian	10%	**Italian**	55%
Caucasian	40% to 70%	**Japanese**	10%
Chinese	20%	**Korean**	10%
Egyptian	80%	**Spanish**	55%
German	50%	**Thai**	25%

Routes of excretion

- Kidneys via urine
- Liver via bile and into feces
- Lungs via exhaled air
- Saliva, sweat, and tears

Excretion

Drug excretion refers to the elimination of drugs from the body. Most drugs are excreted by the kidneys and leave the body through urine. Drugs also can be excreted through the lungs, exocrine (sweat, salivary, or mammary) glands, skin, and intestines via bile and feces.

Half-life

Knowing how long a drug remains in the body helps determine how frequently a drug should be given. Usually, a drug's rate of loss from the body can be estimated by determining its half-life (the time required for the total amount of a drug in the body to diminish by half). A drug's half-life can be determined from a drug concentration-time curve, which plots the drug's concentration level on the vertical axis and the elapsed time in hours on the horizontal axis.

What is half-life?

- The time needed for the total amount of a drug in the body to decrease by 50%

If a patient receives a single dose of a drug with a half-life of 7 hours, the total amount of the drug in his body would diminish by half after 7 hours. The drug amount would continue to decrease accordingly with each subsequent half-life. Most drugs essentially are eliminated after five half-lives because the amount remaining is too low to exert any beneficial or adverse effect.

The importance of five half-lives

- A drug that's given only once is eliminated almost completely after five half-lives.
- A drug that's given regularly reaches a steady-state level after five half-lives.

Although a drug that's given only once is eliminated almost completely after five half-lives, a drug that's given regularly reaches a steady concentration, or steady state, after about five half-lives. Steady state occurs when the amount of drug given equals the amount of drug excreted.

After reaching a steady state, the drug level will fluctuate above and below the average level. This means that, although the drug was once at steady state, its concentration level doesn't remain uniform. Rather, it increases, peaks, and declines within a constant range.

For some drugs, the time required to reach a therapeutic level may be too long to treat an acute problem. For example, digoxin has a half-life of 1½ to 2 days. It could take up to 10 days to achieve a steady-state level to control a life-threatening arrhythmia, such as atrial fibrillation. To reach the desired therapeutic level more rapidly, the patient initially should receive one or more large doses, called loading

doses. He can then receive smaller maintenance doses daily to replace the amount of drug eliminated since the last dose. These smaller doses maintain a therapeutic level in the body at all times.

ONSET, PEAK, AND DURATION

Besides absorption, distribution, metabolism, and excretion, three other factors play important roles in a drug's pharmacokinetics: onset of action, peak level, and duration of action.

Onset of action refers to the time period from a drug's administration to the beginning of its therapeutic effect. The rate of onset varies with the administration route and the drug's pharmacokinetics.

The peak level occurs when the body absorbs more drug, the level rises in the blood, and more drug reaches the site of action. Because some drugs require several doses to reach peak level, it isn't necessarily associated with therapeutic response.

As soon as the drug begins to circulate in the blood, it also begins to be eliminated. Eventually, drug elimination exceeds drug absorption because less of the dose remains to be absorbed. At this point, the drug's level and effects begin to decline. When the level falls below the minimum needed to produce an effect, drug action stops although some drug remains in the blood. Therefore, the duration of action is the length of time that the drug level is sufficient to produce a therapeutic response.

What are onset, peak, and duration?

- Onset of action is the time between when drug is given and when therapeutic effects begin.
- The peak level is the maximum drug level achieved through absorption.
- Duration of action is the length of time a drug produces therapeutic effects.

PHARMACODYNAMICS

Pharmacodynamics is the study of the mechanisms of drug action that produce biochemical or physiologic changes in the body. Drug action — the interaction between a drug and cellular components, such as complex proteins in cell membranes, enzymes, and target receptors — results in the response known as the drug effect.

What is pharmacodynamics?

- The study of the mechanisms by which a drug produces biochemical and physiologic changes in the body

DRUG ACTION

A drug can modify cell function or the rate of function, but it can't impart a new function to a cell or target tissue. Therefore, the drug effect depends on what the cell is supposed to do. A drug can only modify what a cell does by altering the cell's physical or chemical environment or by interacting with its receptors.

Many drugs work by stimulating or blocking drug receptors. A drug can be classified as selective (binding with only one type of receptor) or nonselective (binding with various types of receptors). A nonselective drug can cause many widespread effects.

When a drug binds with and stimulates a receptor, it acts as an agonist, which means that it activates a response. A drug's ability to initiate a response after binding with the receptor is referred to as intrinsic activity. When a drug binds with but doesn't stimulate a receptor, it acts as an antagonist, which means it displays no intrinsic activity and, therefore, prevents a response from occurring.

Antagonists can be competitive or noncompetitive. A competitive antagonist competes with the agonist for receptor sites. Because this type of drug binds reversibly with receptor sites, giving larger doses of an agonist can overcome the antagonist's effects. A noncompetitive antagonist binds with receptor sites and always blocks the effects of the agonist no matter how large its dose. Giving larger doses of the agonist can't reverse this type of antagonist's action.

How a drug acts

- Changes cell environment physically or chemically
- Acts as an agonist, binding with and stimulating receptors, which creates a response
- Acts as an antagonist, binding with but not stimulating receptors, which prevents a response