Physical and Occupational Therapy: Drug Implications for Practice

Terry Malone

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Jordan M. Phillips, M.D.

Preface

Pharmacology has not been an integral part of most therapy curricula. The typical therapist has received "bits and pieces" of pharmacologic management training. The concept for this text arose from attempts to present pharmacology to students in entry level curricula and to therapists in advanced clinical programs.

Rehabilitation therapists assume a much greater role in patient management with the advent of diagnostic related groups (DRG), direct patient access to therapy services, specialization of therapy services, and ambulatory surgery. Patients that previously were hospitalized are now cared for at home and in outpatient settings. Therapists must increase their knowledge of pharmacology if they are to provide adequate patient care in these changing environments.

Physical and Occupational Therapy: Drug Implications for Practice is designed for both the student and the practicing clinician. The student will be exposed to basic pharmacology with an emphasis on "how to find the answers," while the clinician will gain perspective on how pharmacology impacts specialty areas. Generic names for drugs are used throughout the text, with trade names appearing in parentheses.

I would like to thank all the dedicated clinicians who shared their expertise in these pages. Without their efforts this text would not have been possible. I would also like to thank their "significant others" who allowed their contributions!

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Contents

Pharmacology 1

Timothy E. Poe

In this chapter an attempt will be made to acquaint the student/practitioner with the general principles of pharmacology and the general classes of drugs used in the treatment of many diseases. Pharmacology may be difficult for some, primarily because of the vast numbers of agents used in the practice of medicine today. For the most part, this chapter will not concentrate on specific agents but, rather, on principles and examples to illustrate them. Also in this chapter sources of drug information are given so that the reader may obtain pertinent drug information when needed.

The word *pharmacology* was derived from the Greek *pharmakon*, which meant *drug, medicine,* or *poison,* and *logos,* meaning *reason,* and *-logy* meaning the *study of.* Thus, one may define pharmacology as the study of the interaction of chemicals with living organisms. Of course, this is usually in the context of using drugs in patients to bring about some desired effect. Drugs may be defined as chemical compounds used in the treatment, prevention, or diagnosis of disease. For example, antibiotics are chemical compounds used to treat various infections; vaccines are considered drugs because they help prevent diseases; and radiocontrast media are considered drugs because they aid in diagnosis of disease.

Pharmacology is often divided into pharmacokinetics and pharmacodynamics. *Pharmacokinetics* deals with the fate of drugs in the body, including absorption, distribution, metabolism, and excretion. One might think of this as what the body does to the drug. *Pharmacodynamics* deals with the actions and effects of the drug on tissues and organs of the body. In other words, pharmacodynamics is what the

drug does to the body. These topics will be dealt with in more detail later in this chapter.

Pharmacotherapeutics is the study of the use of drugs in the treatment, prevention, or diagnosis of disease. This aspect of pharmacology correlates pharmacodynamics with the pathophysiology, microbiology, or biochemistry of the disease.

Pharmacy means the *art* of preparing, compounding, and dispensing medicines. It also is the place where such medicines are prepared, stored, and dispensed. In today's society the pharmacist may rarely compound medicines because most medications are prepared by a pharmaceutical manufacturer. However, emphasis is shifting toward the pharmacist as a provider of drug information and counselor to patients about their medications.

Toxicology is the study of the harmful effects of drugs and chemicals. Most drugs are screened in animals before studied in humans to determine their toxicologic properties.

DRUG NAMES

Sometimes the names of drugs become confusing becasue there are at least three names for every drug. The *chemical name* is usually referred to only in the product circular or original reference materials. It is the chemical description of the drug. For example, the chemical name for acetaminophen is *N*-acetyl-*p*-aminophenol. The *generic*, or *nonproprietary*, name is the name assigned to the drug when it is found to have potential therapeutic usefulness. The nonproprietary name for *N*-acetyl-*p*-aminophenol is acetaminophen. The proprietary name (trade or brand name) is the name given to the drug by the manufacturer and is usually shorter and easier to remember than the nonproprietary or chemical name. Tylenol is an example of a proprietary name for acetaminophen.

PHARMACOKINETICS

To be effective, drugs must get to their site of action, thus, a discussion of pharmacokinetics would be in order. Remember, pharmacokinetics is the absorption, distribution, metabolism, and excretion of the drug (Fig. 1-1).

Drugs usually must reach the systemic circulation to reach their site of action (except for topical or many inhaled drugs). Drugs may be administered by mouth (*p.o.*) or parenterally. Parenteral administration includes intravenous, intramuscular, subcutaneous, and intradermal administration.

The rate and extent of absorption after oral administration are dependent on several factors, including the chemical characteristics of the drug, the oral dosage form (tablet, capsule, solution, etc.), the gastric-emptying time, and sometimes, the *p*H of the stomach and intestine. There are several oral dosage forms available, some of which are discussed in the following paragraph.

Solutions are liquid preparations that contain one or more dissolved drugs, usually in water. Liquid preparations that contain alcohol are either *elixers* or *tinctures*. *Suspensions* are liquid preparations that are composed of finely divided drug particles that will not dissolve into solution. These preparations must be shaken well to obtain a uniform mixture before administration. *Solid dosage* forms include

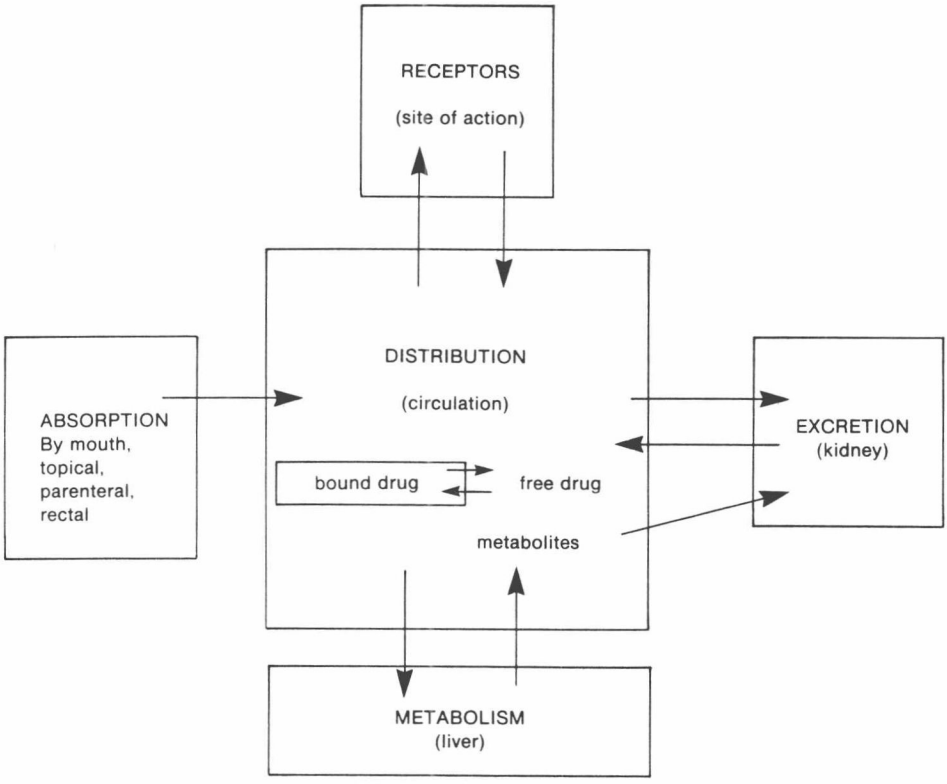

FIGURE 1-1. Schematic representation of pharmacokinetics.

capsules, which contain medication enclosed in a gelatin shell. The shell dissolves in the stomach or intestine releasing the medication for absorption. *Tablets* are solid dosage forms that contain other ingredients (in addition to the medication) to hold them together until they are taken. Tablets are sometimes coated with sugar or other coatings to prevent the patient from tasting the drug and other times are simply compressed tablets (such as most aspirin). One particular type of tablet is made such that it will not dissolve until the drug is in the small intestine. These are referred to as *enteric-coated* tablets. *Sustained-release* preparations are usually capsules or tablets and are made such that not all of the drug is released for absorption at one time. These preparations may enhance compliance because the drug does not have to be administered as often.

Only dissolved drugs can be absorbed from the intestine. Drugs are absorbed most quickly from solutions because these preparations are already in a liquid form and do not have to be dissolved. Slowest absorption would be from a sustained-release product, whereas tablets and capsules have intermediate absorption. *Bioavailability* is the study of the completeness of absorption. It is usually related to the amount of drug absorbed by mouth to the amount administered intravenously. Although the dosage form may make a difference in the bioavailability of a drug, it is usually the characteristics of the drug, itself, that determine

the completeness of absorption. The rate of absorption, however, is more likely to be affected by the dosage form.

Drugs are usually absorbed by simple diffusion. Lipid- or fat- soluble drugs are absorbed more readily than drugs that are more water-soluble. Drugs that have an ionic charge do not pass readily through membranes. Hence, some drugs are affected by *p*H changes in the gastrointestinal tract and may not be absorbed as well. An example of this is a drug that is a weak acid. Aspirin is a weak acid that in the acidic environment of the stomach is relatively un-ionized. This aids absorption in the stomach and upper portion of the small intestine. If aspirin is administered with an antacid, more will be ionized and, as a result, it will not be absorbed as readily in the stomach.

Gastric-emptying time may also be important in drug absorption. As one might imagine, if a patient has a fast gastrointestinal-transit time, the drug is in contact with the intestinal mucosa for a shorter period and may not be as completely absorbed.

Drugs may also be administered *sublingually* (under the tongue) or *bucally* (between the cheek and gum) for rapid absorption. The drug usually administered in this manner is nitroglycerin, given for angina pectoris.

Parenteral administration of a drug is required usually when a patient needs a more immediate effect, the patient cannot take the drug by mouth, or the drug is not absorbed when taken orally. The quickest way to get the drug into the circulation is to inject the drug directly into the venous circulation, hence, intravenous injection. Drugs are rapidly distributed and, generally, quickly reach their site of action. The disadvantages of this method are that sterility of the drug and a sterile technique must be preserved, and caution must be taken not to administer too much drug because it would be particularly easy to produce dangerously high drug levels. *Intramuscular injection* (into a muscle mass) also requires sterile procedures. Relatively rapid absorption is obtained because of good blood supplies in muscle, but this absorption is not as rapid as with intravenous injection. This form of administration is useful when suspensions of drugs must be given, such as with procaine penicillin given for an infection. *Subcutaneous injection* is giving the drug under the skin between the skin and the muscle mass. Absorption is slower from subcutaneous tissue than from muscle. Drugs such as insulin are usually administered subcutaneously. As with other injections, sterility must be maintained. Drugs that are suspensions may be given either subcutaneously or (usually) intramuscularly to produce a sustained-release effect (Table 1-1).

After absorption, the drug is carried in the blood to its site of action. This is known as the *distribution phase.* Not only is the drug taken to its site of action, but it may also be distributed into other areas of the body, such as the central nervous system and adipose tissue. Generally, the smaller the molecular makeup and the more lipid-soluble it is, the better the drug is able to penetrate tissues and the more widely distributed it becomes. Drugs such as anesthetics (very lipid-soluble) are widely distributed and penetrate the central nervous system quite rapidly.

Transportation in the blood is facilitated by binding of the drug to serum protein, usually albumin. This is occasionally a problem with two or more drugs that compete for the same binding site, causing higher "free" levels of one of the drugs and more drug effect. *Free drug* is that portion of the total drug in the plasma that is not bound to plasma protein, whereas *bound drug* is the portion that is bound to the protein. Only free drug can penetrate capillary walls to reach its site of action. Once

TABLE 1-1
Routes of Administration

Route	Speed of Absorption*	Comments
Oral	+	Usually most convenient; nonsterile
Sublingual	++	Convenient; nonsterile; bypass liver, direct to circulation
Buccal	++	As for sublingual
Rectal	+ to ++	Bypass liver; not convenient; may irritate rectal mucosa
Subcutaneous	++ to +++	Sterility necessary; painful; may be used in unconscious patient; may be used for soluble and insoluble forms
Intramuscular	+++	More rapid absorption (blood supply good); sterility necessary; may be used in unconscious patient; may be used for soluble and insoluble forms
Intravenous	++++	Directly into circulation; most rapid absorption; sterility necessary; must use soluble forms

*Author's opinion. Speed of absorption is variable, depending on dosage form used. This is a rough comparison to give the student an overall idea of differences in absorption from various sites.

a drug is in the plasma, an equilibrium is set up such that as a drug is eliminated or reaches its site of action, more drug is released from albumin.

The magnitude of distribution is measured in terms of volume of distribution, which is a hypothetical volume that shows the relationship between the available drug and the serum concentration. The *volume of distribution* is that volume, or apparent volume, of fluid through which the drug would have to be distributed to produce the existing serum concentration.

Drugs are eliminated from the body by two primary mechanisms, metabolism and excretion. *Metabolism* is the process of transforming drugs into more water-soluble compounds so that they may be excreted by the kidneys. Metabolism takes place chiefly in the liver, although other organs may sometimes be involved, such as the kidneys and circulatory system. Although metabolism of drugs by the liver usually changes active drugs into inactive compounds, a few drugs are not active until transformed by the liver. In fact, most drugs are *detoxified* in the liver; however, in some rare instances, metabolites may be more toxic than the parent compound. Many drugs are both metabolized by the liver and excreted unchanged by the kidney. The most common drug biotransformation reactions include oxidation, reduction, hydrolysis, and conjugation. Many drugs are metabolized by the microsomal mixed-function oxidase enzyme system in the liver. This is important because these enzymes are inducible and some drugs may stimulate the metabolism of other drugs. The opposite is also true, some drugs may decrease the metabolism of the other, resulting in higher-than-normal levels. Some drug interactions occur by this mechanism.

Excretion of drugs or their metabolites is carried out by the kidney by two processes, *glomerular filtration* and *tubular secretion.* Drugs that are simply filtered

through the glomerulus may be carried through the tubule into the urine or, to some extent, reabsorbed, depending on the drug's lipid solubility and *p*H of the urine. Other drugs are eliminated by active secretion by the tubule into the urine. In any event, it should be obvious that patients with decreased kidney function (for example, renal disease or elderly patients) may have problems eliminating certain drugs that are primarily excreted unchanged in the urine. Drugs may also be excreted in other body fluids, such as milk, saliva, and sweat, as well as in feces.

Although the major processes of pharmacokinetics have already been discussed, several other terms and principles need to be appreciated. The rate of disappearance of a drug from the body, whether by metabolism, excretion, or a combination, is known as a drug half-life. The *half-life* of the drug may be defined as the time it takes for half the drug in the body to be eliminated. Most of the time it is measured in hours; however, for some drugs the half-life is measured in days and, for others, in minutes. The half-life of a drug is useful information to determine how long the drug "hangs around" in the body. Not only would it tell us something about how long the drug remains in the body, but it also gives us some indication on how often to administer some drugs. The dosage interval for many drugs (mostly those that are not sustained-release) is equal to the half-life.

Drugs tend to accumulate in the body if given on a regular schedule until the amount eliminated is equal to the amount administered. This is called the *steady state* and is usually reached after five half-lives of the drug have passed, assuming the drug has been administered regularly. It is important to realize that drugs with long half-lives may take several days to weeks to reach steady state. For example, digoxin, a medication used to treat congestive heart failure, has a half-life of approximately 44 hr in an individual with normal kidney function. If the patient is not given a loading dose, he may not reach the final serum concentration equilibrium (steady state) for 10 days.

PHARMACODYNAMICS

The study of pharmacodynamics provides information on how drugs bring about their effects on the body. In general, drugs act by forming a bond, usually reversible, with some cellular constituent (receptor). Most drugs act on a specific receptor. Drugs that react with a receptor and elicit a response are called *agonists*, whereas drugs that act on a receptor and prevent the action of agonists are called *antagonists*. The typical example of this action is the histamine–antihistamine interaction. Antihistamines block the action of histamine (to produce all those symptoms of hay fever) by attaching to the histamine receptor and blocking the binding of histamine. *Partial agonists* also exist and are drugs that bind with a receptor but cannot produce maximal response compared with an agonist.

Two confusing terms are potency and efficacy. *Efficacy* is the capacity to stimulate or produce an effect for a given receptor occupancy. In other words, how well the drug works. *Potency* refers to the dose required to produce a given effect relative to a standard. Many times the use of the word *potency* misleads one into believing that because a drug is more potent, it is more effective. For example, morphine, 10 mg, is often compared with meperidine (Demerol), 75 mg. Morphine is the more potent compound because it takes less to produce the same effect as the meperidine, 75 mg.

Drugs may produce their effects in various sites throughout the body. For example, antibiotics produce their effects on the bacteria, wherever it may be, providing the antibiotic can penetrate that particular tissue. Drugs that are diuretics produce an effect because they act directly on the kidney. Some drugs may have an indirect effect, acting on one part of the body but causing an effect elsewhere. Morphine causes constriction of the pupil, not because of a direct effect on the pupil, but because of an effect on the brain. Atropine, on the other hand, acts directly on the muscle of the iris to cause dilation of the pupil.

Drugs may act *extracellularly*, at the surface of the cell, or *intracellularly* to exert their effect. Examples of drugs that act extracellularly are antacids, which neutralize excessive gastric acid; and heparin, which decreases the ability of the blood to clot. Drugs such as antihistamines act at the cellular level by interacting with a receptor to block the effects of histamine. Some drugs, such as anesthetics, act at the cellular level by nonspecifically interacting with cell membranes. Other drugs, such as antibiotics that interfere with normal growth and reproduction of the bacteria, act intracellularly (inside the bacteria).

The interaction of the drug with the body (site of action) produces some effect. When increasing amounts of drug are required to produce the same effect, *tolerance* has developed. This occurs with some drugs but not with others. Narcotics, alcohol, and barbiturates are well-known examples of drugs that produce tolerance. Rapidly developing tolerance is called *tachyphylaxis*.

Although one would like to have a drug that does only one thing, that is not possible. In addition to the desired action of a drug, there are also undesired effects called *side-effects*. Side-effects can be divided into two categories: predictable reactions and unpredictable reactions. *Predictable* reactions comprise 70% to 80% of all drug reactions and are usually extensions of the pharmacologic effects of the drug. These side-effects are usually dose related, so that as the dose increases so does the number and severity of side effects. These adverse reactions can be repeatedly demonstrated in experimental animals or in human trials. *Unpredictable* reactions may be subdivided into idiosyncratic reactions and allergic reactions. *Idiosyncratic* reactions are unusual or unexpected reactions that do not fit the usual pharmacologic actions of the drug. An example of this type of reaction is hyperactivity from phenobarbital, when the action that is expected is sedation. *Allergic* reactions comprise 6% to 10% of all drug reactions, are not related to the pharmacologic effects of the drug, are unlikely to be related at all to dose, and are not reproducible in studies (except for that individual who had the reaction). Most allergic reactions are manifested by skin reactions and, although uncomfortable (itching, burning, and the like), are not life-threatening. However, *anaphylactic* reactions may occur that result in bronchospasm, hypotension, shock, and death, if not treated quickly.

Drug interaction is a term usually used to describe an adverse event involving the interplay between two or more drugs. Although, by strict definition, an interaction does not have to be adverse, the common usage of this term implies an adverse event. Drugs may interact through pharmacokinetic mechanisms and pharmacodynamic mechanisms. A drug may interfere with the absorption of another (antacids interfere with the absorption of tetracycline), the distribution of another (displace another agent from albumin-binding sites), decrease or increase metabolism of another agent (cimetidine decreases the metabolism of drugs such as warfarin), or excretion of the other agent (probenecid blocks the excretion of penicillin, usually, a good interaction). Pharmacodynamic interactions involve the effects of the

drug, rather than serum levels. For example, certain tricyclic antidepressants block the uptake into the cell of some antihypertensives, rendering the antihypertensive ineffective.

DRUG SAFETY AND EFFECTIVENESS

Before a drug can be given to a human, it must be undergo extensive toxicity testing in animals. Both acute and chronic toxicity studies are conducted in two or more species of animals. *Acute* studies attempt to identify organs or tissues affected by the drug and to determine the lethal dose. *Chronic* toxicity studies over long periods look at the likelihood that the drug may cause problems when used over an extended period, particularly the drug's carcinogenic potential. Drugs are also tested for teratogenic potential (ability to cause birth defects) in animals.

After a drug is thoroughly studied in animals, human studies are conducted. Unfortunately, there is a lack of total correlation between toxicity data in animal studies and adverse effects in humans. However, because of some similarities and because it is the "best we have" animal studies are a necessity. Human studies are conducted to determine the efficacy as well as the safety of the drug. New drugs are usually compared with drugs already in use to determine their comparative efficacy in addition to comparing them with placebo. Double-blind studies are usually necessary to eliminate patient and investigator bias. Adverse events are reported to the company conducting the investigation and, providing the drug is safe and efficacious, appear in the product package circular.

When drugs are marketed, they fall into one of two classes; *prescription* (legend) drugs or *nonprescription* (over-the-counter, or OTC) products. Prescription drugs are those that require a prescription from an authorized practitioner for their use. The term *legend* refers to the required label on the package stating: "Caution: Federal law prohibits dispensing without prescription." Drugs that are considered prescription drugs generally belong to one or more of the following categories: (1) drugs that are habit-forming and certain hypnotics; (2) drugs that are not considered safe enough for self-medication by the lay public; and (3) drugs that may not be considered safe for indiscriminate use. The OTC drugs are those determined to be safe enough for self-medication.

Drugs that have a high likelihood of being abused are not only prescription drugs, but also more rigidly controlled. These drugs are regulated under the Controlled Substances Act and termed controlled substances. Examples of controlled substances are narcotics (morphine, codeine, meperidine), barbiturates (pentobarbital, secobarbital, phenobarbital), amphetamines, and other substances that are likely to be abused. Controlled substances are divided into five classifications (Schedule I–Schedule V) and penalties for illegal use differ among them (Table 1-2).

SOURCES OF DRUG INFORMATION

With the vast amount of information available on drugs and their use, it is important to realize that even the most knowledgeable person must consult the literature frequently. Many different information sources are available. Some of the more frequently consulted sources, as well as some less well known but valuable resources, are discussed in the following paragraphs.