Section 1: Mechanism of Action and Pharmacokinetics: General Principles

MECHANISM OF ACTION
The mechanisms by which drugs manifest their pharmacologic effects are sometimes known with certainty and, at other times, they are obscure. In some cases, the mechanism of action is obvious, for instance, when the drug replaces a missing biochemical substance, such as insulin for diabetes. In other cases, the mechanism is more complex, but still known, for instance, allopurinol inhibits an enzyme necessary for the formation of uric acid. By decreasing the concentration of uric acid in the blood, allopurinol relieves gout. Sometimes the mechanism of action of a drug is unknown, even though the drug has been used for a long time, for example, the role played by phenytoin in decreasing epileptic seizures is not known.

Many drugs interact with receptors (proteins) in the body to produce their effects. The affinity of a drug for certain receptor sites (either on or within the cell) and the response produced is related to its chemical structure and the action at the receptor site. The drugs that are not receptor mediated produce their effects by simple chemical or physical interactions with local molecules such as that seen with antacids, laxatives, and antiseptics. In the Nurse’s Drug Handbook, a drug’s mechanism of action is provided when it is known.

PHARMACOKINETICS
Pharmacokinetics is the study of the fate of drugs in the body. This science concerns itself with:

- Drug absorption and distribution
- Drug plasma concentration
- Therapeutic plasma levels
- Toxic plasma levels
- Concentration of the active drug at the target site
- Rate of metabolism
- Rate of excretion

These parameters, in turn, are affected by:

- Physiochemical nature of the drug (e.g., lipid solubility)
- Dosage form of the drug
- Route of administration
- Extent of binding of the drug to plasma and/or tissue proteins (bioavailability)
- Individual characteristics of the client
- Concomitant diseases
- Concomitant administration of food or other drugs

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Pharmacokinetics has assumed great importance in medicine because many clients are currently taking an increasing number of potent drugs, often concomitantly and for prolonged periods of time. Pharmacokinetic concepts that play a major role in the administration of drugs include administration, absorption, onset of action, peak of activity, half-life, first-pass effect, drug distribution, drug elimination, therapeutic serum levels, bioavailability, and therapeutic drug delivery systems (such as lipid or polymer-based nanoparticles designed to improve parenterally administered drugs’ therapeutic and pharmacologic properties.

Known pharmacokinetic data, as well as mechanisms of action of drugs, are included in the discussions of individual drugs or drug classes in the Nurse’s Drug Handbook. The information listed for the various drugs is neither complete nor entirely consistent. Pharmacokinetic data are lacking for some of the older drugs still widely used today. Moreover, data obtained from the literature and/or from drug manufacturers are often inconsistent and spotty. Onset of action is given for some drugs; time to attain peak serum levels or therapeutic serum levels is listed for others whenever known. Consistency was sacrificed for completeness of information. When available and/or known, we have listed all or some of the following:

- Mechanisms of action
- Onset of action
- Therapeutic serum levels
- Duration of action
- Metabolism/excretion
- Time to attain peak serum levels
- Biologic half-life (t½)
Administration

The route used to administer drugs has a profound effect on drug absorption, distribution, metabolism, and elimination (Figure 1-1).

**Oral (Enteral) Administration.** Oral administration is the most economical, easiest, and most widespread route. Drug absorption after oral administration is affected by the presence of food, other drugs, gastric emptying time, intestinal motility, the pH of the stomach and intestine, the nature of the drug (e.g., small, lipid-soluble molecules are absorbed more quickly than others), the rate of disintegration and dissolution of the tablet or capsule (affected by physical state and coating), and blood circulation to the gastrointestinal (GI) tract. Importantly, certain drugs cannot be given orally at all (without special protective measures) because they are destroyed by stomach acid (i.e., insulin). Some orally administered drugs are degraded partially by various enzymes in the GI tract, in the intestinal mucosa, and most of all, in the liver (see First-Pass Effect). A combination of all or some of these factors could be responsible for only a fraction of orally administered drugs becoming absorbed into the bloodstream (see Onset of Action and Peak of Activity). Forms include tablets, enteric-coated tablets, capsules, timed-release (sustained release, extended-release) capsules, lozenges (troches), suspensions, emulsions, elixirs, fluid extracts, syrups, and solutions.
Intramuscular and Subcutaneous Administration. Drugs are absorbed into plasma from intramuscular (IM) or subcutaneous (SC) injection sites by simple diffusion. Larger molecules (e.g., proteins) are absorbed through the lymphatic circulation. Absorption is prompt. Duration of action can be increased with the use of formulations that decrease the rate of absorption. Forms include solutions and powders. The IM route is slow to absorb and painful, and is not used very often anymore.

Intravenous Administration. Intravenous (IV) administration ensures prompt onset of action and eliminates the uncertainty associated with the incompleteness of drug absorption by other routes. IV administration is the only route that can be used for certain irritating drugs or solutions because the walls of blood vessels are relatively resistant to irritation. IV administration usually requires careful preparation with attention to dilution, rate of administration, and close monitoring by the nurse because this route increases the risk of toxic or other serious side effects. Forms include solutions and powders. IV is the fastest way to get drugs into the body.

Sublingual Administration. Drugs placed under the tongue are absorbed rapidly into the venous circulation; this method of drug administration avoids the first-pass effect of the liver. This method is only suitable for certain highly active agents, such as nitroglycerin.

Rectal Administration. Rectal administration is sometimes used when oral administration is precluded (e.g., in cases of severe vomiting or unconsciousness). Absorption can be slow and uncertain. One advantage to rectal administration is that the drug is absorbed in the GI tract below the portal vein and thus avoids the first-pass effect of the liver. Use of this route is limited because many drugs are irritating to the rectum. Forms include suppositories, enemas, and tablets. Do not use with GI bleeding or with thrombocytopenia.

Intracavitary Administration. Intracavitary administration (within an organ or body cavity) is useful for certain antineoplastic agents because this route specifically increases the concentration of the drug at the site of action. Forms include liquids and powders.

Mucous Membrane Administration. Mucous membrane administration is usually restricted to localized therapy, although it is used occasionally for systemic administration (e.g., antidiuretic hormone). Absorption can be rapid. This route includes intranasal, inhalation, intrapulmonary endotracheal, buccal, and intravaginal administration consisting of powder, drops, sprays and gels.

Skin (Cutaneous) Administration. Intact skin is relatively impermeable to most drugs; therefore it is a good route for achieving localized results in various skin conditions. Absorption is increased if the skin is abraded or denuded, if the drug is added to a specific solvent, or if medicated skin is covered by an occlusive dressing. Also, if a drug is applied over a large surface area of the skin and for a prolonged period of time, systemic effects may be observed. Forms include liquid, gel, cream, and lotion.
**Therapeutic Drug-Delivery Systems.** In therapeutic drug-delivery systems, a pharmacologic agent is delivered continuously from a reservoir for prolonged periods of time such as a patch (e.g., Lidoderm, fentanyl patch). With fentanyl, which is lipophilic, the client must weigh at least 115 pounds in order for the medication to be absorbed.

**Intrathecal Administration.** The injection of a drug directly into the spinal subarachnoid space is necessary for the administration of certain drugs used for the treatment of spasticity, pain, meningitis, and related disorders. Access to their site of action is precluded or diminished because of the blood-brain barrier. Absorption is rapid. Use of health care professionals specifically trained in intrathecal administration of drugs and pump maintenance and care is necessary because of the special administration techniques required and the potential for contamination. Form is a solution by an implantable pump or external pump.

**Other Delivery Systems (DDS)**

**Transscleral and Intravitreal DDS.** Can deliver therapeutic concentrations of drug and ↓ systemic exposure

**Surgically Implanted Medication Delivery Systems** such as pain balls and disposable implanted pumps

**BioErodible MucoAdhesive (BEMA) Delivery System.** Multilayered disk delivers local or systemic levels of drug across mucosal tissue; prevents drug deactivation by avoiding first-pass liver metabolism

**Nanotherapy.** This delivery system may be in the near future. Targeted drug delivery to specific organs, cells, tissues using nanoparticles to improve delivery and drug uptake. Drugs can be encapsulated or coupled into nanoparticles. Nano shells are hollow silica spheres coated with gold, silver or other metals equipped to carry antibodies to enhance retention and may be triggered externally. Implantable biosensing microchips

**Absorption**

The rate of absorption of a drug is of paramount importance because it is reflected in the concentration of the drug in the serum and at the target site. It determines the drug’s time of onset of action and the time of peak effect. If absorption is too slow compared with elimination, the drug might never attain the minimum effective therapeutic serum concentration (Figure 1-2). In addition to being affected by the route of administration, absorption is also affected by:

- Formulation of the drug (tablets versus capsules, use of liquid products, inert additives, coatings, drug-delivery systems)
- Character of the drug itself (e.g., acidic versus basic)
- Drug solubility
- Presence or absence of food (oral administration)
- Client characteristics: age, body weight, individual factors, ethnic background, presence of concomitant disease

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The customary manner of diagramming drug absorption by plotting serum concentration as a function of time is shown in Figure 1-2.

![Figure 1-2](image)

**Figure 1-2. SOURCE: DELMAR/CENGAGE LEARNING**

**Onset of Action**
The onset of action refers to the time interval between administration of the drug and notation of the first therapeutic effects (see Figure 1-2). It depends on the route of administration, the characteristics of the drug, its rate of absorption through various membranes, and the formulation (how fast the drug is released into the system from the dosage form). The onset of action is especially variable after oral administration, depending on the presence of food in the stomach, the motility of the GI tract, and other factors.

**Peak of Activity**
The peak of activity, when the drug reaches its maximum effect, coincides often (but not always) with peak serum concentration (see Figure 1-2). This peak may surpass the optimally effective level, leading to toxic effects, but the concentration can fall rapidly below this level as a result of biotransformation and excretion. This drop occurs especially when a short-acting drug is given initially or intermittently. In the treatment of diabetes, for example, insulins with various lengths of action are mixed to keep insulin levels at a therapeutically effective level around the clock (fasting and postprandial blood sugars).
Biologic Half-Life ($t_{1/2}$)
The time in which half the drug has been eliminated is the biologic half-life or $t_{1/2}$. If no additional drug is administered, it takes two half-lives to eliminate 75% of the drug and four half-lives to eliminate 93.3% of the drug.
In practice, most drugs are administered more than once; a subsequent dose is administered generally before the previous dose has been fully eliminated. This overlap can result in drug accumulation. The biologic half-life is an important concept in establishing dosage frequency. In general, a dosage interval equal to, or less than, the $t_{1/2}$ is recommended for most drugs. Thus, if $t_{1/2}$ is 4 hours, the drug can be given up to six times per day. In practice, an attempt is made to consider the convenience of the client in setting dosage schedules.

Most drugs have a short half-life (e.g., anesthetics). Other drugs, the monoamine oxidase inhibitors (MAOIs), for example, have exceedingly long half-lives of days to weeks.

The concept of half-life is important in all aspects of drug therapy, including the treatment of drug overdosage. The opioid antagonist naloxone, for example, has a shorter $t_{1/2}$ than that of morphine; therefore, administration of the antagonist must be repeated until the effects of the opioid have worn off. The concept of half-life can only be applied to the drugs when they have been absorbed into the blood circulation and not to those applied topically.

Half-life, as well as other pharmacokinetic factors, varies with the age of the client, concomitant diseases (especially renal or hepatic impairment), and the presence of food and/or other drugs. Sometimes a drug (or its active metabolites) is eliminated in two or more stages. In such cases, $t_{1/2}$ is said to be biphasic or multiphasic. This is important for nurses to be aware of especially when administering a drug with a long half-life such as methadone. There have been several cases of oversedation with this drug.

First-Pass Effect
Most toxic substances, including drugs, are degraded by the microsomal enzymes of the liver. Because orally administered drugs are absorbed from the GI tract into the hepatic circulation, they must pass through the liver before they can reach the general circulation and their target. This effect can result in a considerable loss of activity of the administered drug, a phenomenon referred to as the first-pass effect. The first-pass effect is taken into account when drugs are formulated, that is, a higher concentration must be administered orally rather than parenterally. Note that when drugs are administered sublingually or rectally, they do not have a first pass through the liver, but enter the general circulation directly (see Figure 1-1).

Distribution
The distribution of drugs in the body is governed by the physiochemical characteristics of the specific drug. The speed by which a particular agent is absorbed throughout the various biologic membranes depends on such factors as the size of the molecule, its solubility, and the pH of the tissues.
Many drugs are distributed in the body tissues; however, once the drug has been injected into, or has reached, the bloodstream, it attains significant concentrations first in such highly perfused organs as the heart, liver, and kidneys (within minutes). Delivery of the drug to the viscera, skin, and adipose tissue is slower (minutes to hours). Penetration of some tissues is even slower, and the distribution phase can be extremely slow for drugs that bind strongly to serum proteins because the drug-protein complex is unable to pass out of the plasma. This has prompted the research into other drug delivery systems. Distribution of certain pharmacologic agents to the central nervous system (CNS) is often limited because the blood-brain barrier is selective in admitting compounds. The ability of a drug to reach the fetus depends on its ability to cross the placental barrier.

Elimination
A crucial parameter from a therapeutic point of view is the time it takes for a drug to be eliminated from the body. Elimination rates are determined experimentally on a number of test subjects, and the rate cited in the literature represents an average. Drug elimination is a composite of drug metabolism, which can result in active or inactive metabolites, and drug excretion.

Metabolism. Metabolism is the sum total of all the reactions involved in the biotransformation of a pharmacologic agent after it is administered. Most metabolic transformations are enzymatic and occur in the liver, although some drugs are metabolized in other organs, such as the kidneys, or even in the plasma. A decreased rate of drug metabolism will result in the presence of liver disease, thereby requiring a decrease in dosage. In contrast, prolonged administration of certain drugs (barbiturates, phenytoin, alcohol) increases the efficacy and/or concentration of certain drug-metabolizing hepatic enzymes (enzyme induction). This results in an increased rate of metabolism of certain drugs. In such cases, a higher dose of these drugs might be required to attain and/or maintain the drug at effective therapeutic levels. Metabolism often increases the water solubility of the pharmacologic agent and facilitates renal excretion. It is important to note that sometimes metabolism is required for the drug to become active and therefore exert its pharmacologic effect. In other instances, metabolism might convert the drug to a more toxic compound.

Excretion. The vast majority of drugs and/or their metabolites are excreted through the urine, although a number of drugs are excreted by the bile (e.g., chlorpromazine, salicylates, steroid hormones, antibiotics). After entering the intestine in the bile, the drug is reabsorbed and re-enters the blood and again is carried to the liver (called enterohepatic cycle). Drugs excreted in the bile are eliminated eventually from the body in the feces. A few agents are excreted via the lungs (e.g., volatile anesthetics, such as nitrous oxide, halothane, isoflurane). Small amounts of drugs can also appear in the saliva and sweat and can cause skin rashes. Drugs can find their way into breast milk and, therefore, will be ingested by the infant. Thus, the benefits versus the risks of the mother continuing to nurse when taking a drug known to cause toxic effects should be evaluated carefully.
The rate of renal excretion is determined by the glomerular filtration rate (GFR), tubular reabsorption, and tubular secretion. In general, the more lipid-soluble a substance is, the slower its renal excretion (i.e., the drug is reabsorbed from the kidney tubule). When elimination is slow or slowed because of renal disease the risk of drug accumulation and drug toxicity is increased. Note that dosage is reduced for most drugs in the presence of impaired renal function; in fact, some drugs cannot be given if the client has impaired renal function. When available, data on excretion are listed as percentage urinary excretion. Many drugs are excreted unchanged (chemically identical to the drug administered) by the kidney (e.g., digoxin).

**Therapeutic Serum Levels**

Therapeutic serum level refers to the concentration of the drug in the serum at which its therapeutic action is manifested. Ideally, the optimal concentration should not be exceeded and should be maintained for prolonged periods of time. In practice, the administration of conventional dosage forms results intermittently in drug concentrations that sometimes exceed or fall below the minimal or optimal dosage levels. Examples include:

- Certain antibiotics, because growth of most microorganisms is only inhibited above certain serum drug levels (the minimal inhibitory concentration, or MIC)
- Drugs in which there is a narrow margin between a therapeutic effect and a toxic effect (e.g., digitalis, phenytoin, lithium)

**Bioavailability**

The bioavailability of a drug measures the concentration of the pharmacologically active substance at the target site and/or in the serum. Bioavailability is a function of:

- The drug content itself
- The metabolism of the client
- The rate at which the drug is liberated from its dosage form or from storage in the body proper

For example, many drugs bind to serum proteins (plasma albumin in particular), from which they are released gradually; other drugs are stored in specific organs, in adipose tissue (lipid-soluble drugs, such as thiopental), and even in bone (tetracycline). Some of these factors are of such magnitude that substitution of one preparation of a specific drug for another can affect bioavailability. For example, the rate of disintegration of tablets of the same drug made by different manufacturers may be significantly different.

A drug is said not to be bioavailable if, or to the extent that, it is:

- Bound to protein or to any other substance that renders the drug permanently or temporarily inactive
- Not released from its dosage form or site of administration
- Partially or totally degraded
Protein binding plays a major role in drug interactions because when two drugs are administered concomitantly, one drug (drug A) might have a greater affinity for protein than drug B. This action increases the concentration (bioavailability) of drug B in the blood and tissues, sometimes producing an increase in the duration and/or intensity of its effect. If this occurs a dosage adjustment is necessary.

Bioavailability is taken into account by the manufacturer in establishing dosage levels. To attain the desired therapeutic dosage levels, drugs that bind tightly to serum protein and are released slowly, are given at a higher dosage and less frequently than a drug that is immediately available and that is degraded or excreted rapidly.

**Therapeutic Drug-Delivery Systems**

The drug serum concentration that results from drugs administered as conventional preparations (tablets, injections) undergoes wide fluctuation, especially when the pharmacologic agent is metabolized and/or excreted rapidly (i.e., has a short t_{1/2}). For drugs with a short t_{1/2}, excessively high doses must be given and/or a high frequency of administration must be used to maintain a drug blood concentration at or above the effective therapeutic level. Administration of high levels of medication is undesirable, however, because most drugs have toxic and/or unpleasant side effects at higher dosages. Unfortunately, clients sometimes fail to comply with orders for repeated drug administration (e.g., several times per day for a period of time). However, constant blood levels of drugs may be desired to prevent the occurrence of disease symptoms such as angina or motion sickness.

This difficulty has been partially overcome with the development of sustained-release preparations in which the drug is released in stages. Such preparations often consist of hundreds of small pellets coated with materials that dissolve at different rates. The drug is incorporated into tablets with varying layers with each layer disintegrating at a different time after oral administration, or the drug is impregnated into a matrix on a patch and the drug is then slowly released. The development of drugs with long half-lives, which by their nature have to be administered less frequently, may also be possible.

Another mechanism to ensure that adequate therapeutic serum levels are maintained is administration via IV drip. This method is used, for example, when antibiotics are administered to combat life-threatening infections. A similar principle underlies the therapeutic systems that deliver a drug continuously for a period of hours, weeks, or even months. Small drug reservoirs, enclosed in semipermeable membranes, are inserted into or applied near the target site. The drug diffuses out of these systems into the body; the rate can be adjusted ideally so that input equals output (rate of excretion). Such therapeutic systems are especially suitable for drugs that have a short t_{1/2} and are required at low doses or for maintaining constant blood levels of drugs for prolonged periods of time. Examples of such systems include:

- Fentanyl Transdermal System, which provides continuous delivery of analgesic for up to 72 hours (drug is lipophilic; client must weigh > 115 lb.)
- Estraderm, which delivers estradiol for approximately 3 days
- Lacrisert, which delivers a moisturizing agent for dry eye syndrome
- Ocusert, which delivers pilocarpine into the conjunctival sac for 1 week
- Deponit, Nitrocine, Nitrodisc, Nitro-Dur, Transderm-Nitro, all of which deliver nitroglycerin for 24 hours
- Progestasert, which delivers progesterone from an intrauterine device (IUD) for about 1 year
- Transderm Scop, which delivers scopolamine for 3 days

**Biotechnology**

Techniques are currently available to develop drugs using concepts of molecular biology. Through genetic engineering (e.g., recombinant DNA), a number of drugs have been marketed, including human insulin, interferon alphas and gamma, growth hormone, alteplase (a thrombolytic agent), and colony-stimulating factors (e.g., filgrastim and sargramostim).

The impact of such technology is just beginning to be appreciated. It is now possible to design drugs for specific diseases and to synthesize naturally occurring human hormones (e.g., insulin). Such processes allow for the production of pure products, for example, genetically engineered human insulin is indistinguishable from naturally occurring insulin, thus virtually eliminating the chance of side effects or tolerance.

At the present time all of the drugs developed through genetic engineering must be injected, except nasal insulin. Thus, it is becoming increasingly important for clients to know the correct method for administration of these drugs. Also, it is likely that new methods for drug administration will be available (e.g., nasal sprays, use of antibodies, and nanoparticles, nanoshells in the very near future – See administration).

**Drug Testing**

Before a drug can be marketed in the United States, extensive testing is necessary, in both animals and humans, to ensure safety and effectiveness. The Food and Drug Administration (FDA) is the federal agency charged with regulating the testing, marketing, and advertising of drugs in this country.

Testing of a potentially new drug always begins in animals; however, animal studies cannot always predict what effects human clients will manifest. Thus, initial drug testing in humans does carry a certain amount of risk. To protect human subjects in such studies, institutional review boards (IRB) for human subjects and the informed consent form have been established. Recently there have been exceptions to this procedure to bring drugs rapidly to the market for certain conditions (e.g., AIDS, terminal cancer).

The IRB functions as a body to review proposed drug studies in humans to determine if the studies are sound ethically, medically, and scientifically. Informed consent must be obtained from all humans participating in drug studies. The consent form details, in language easy to understand, the nature of the study; the type of drug to be used; and any potential benefits, risks, or side effects. Subjects should be told that participation is voluntary and that they can withdraw from the study at any time without any negative repercussions. Opportunities should be made available for subjects to ask questions.
After extensive laboratory and animal study, drug development in humans usually occurs in the following phases:

**Phase I Clinical Pharmacology.** These studies are usually conducted in healthy men and some women between the ages of 18 and 45 years (women who are in their childbearing years are not used because the drug can affect the fetus if the woman becomes pregnant). The purpose of Phase I studies is to determine the dose level at which symptoms of toxicity occur.

**Phase II Clinical Investigation.** In these studies the drug is administered to clients with the specific condition for which the drug is intended. The goal is to determine the effectiveness of the drug and to establish the optimum dose and dose range.

**Phase III Clinical Trials.** If serious side effects have not occurred during Phase II, and if the optimum dose range has been established, the drug is administered to large numbers of clients (hundreds to thousands). The goal is to make sure the drug is effective and to uncover any side effects that were not discovered in Phases I and II.

**Phase IV Postmarketing Studies.** Such studies are undertaken for continuing evaluation of the drug, especially in clients who are usually excluded from Phases II and III (e.g., geriatric clients, children, and women of childbearing age). Also, these studies continue to monitor for the occurrence and frequency of side effects.