

Pharmacokinetics

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I. OVERVIEW

Pharmacokinetics refers to what the body does to a drug, whereas pharmacodynamics (see Chapter 2) describes what the drug does to the body. Four pharmacokinetic properties determine the onset, intensity, and the duration of drug action (Figure 1.1):

- **Absorption:** First, absorption from the site of administration permits entry of the drug (either directly or indirectly) into plasma.
- **Distribution:** Second, the drug may then reversibly leave the bloodstream and distribute into the interstitial and intracellular fluids.
- **Metabolism:** Third, the drug may be biotransformed by metabolism by the liver or other tissues.
- **Elimination:** Finally, the drug and its metabolites are eliminated from the body in urine, bile, or feces.

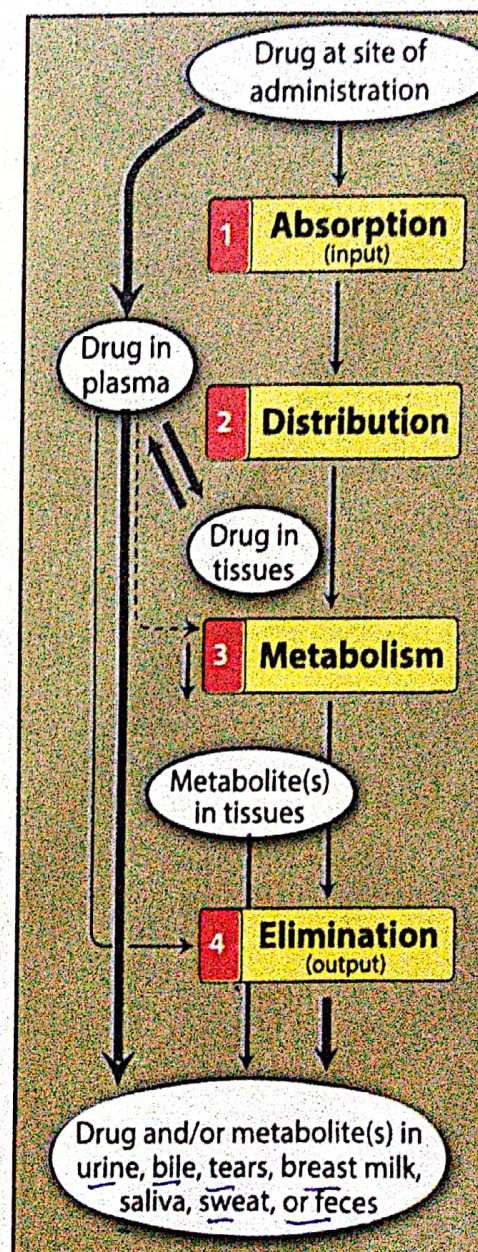
Using knowledge of pharmacokinetic parameters, clinicians can design optimal drug regimens, including the route of administration, the dose, the frequency, and the duration of treatment.

II. ROUTES OF DRUG ADMINISTRATION

The route of administration is determined by the properties of the drug (for example, water or lipid solubility, ionization) and by the therapeutic objectives (for example, the desirability of a rapid onset, the need for long-term treatment, or restriction of delivery to a local site). Major routes of drug administration include enteral, parenteral, and topical, among others (Figure 1.2).

Figure 1.1

Schematic representation of drug absorption, distribution, metabolism, and elimination.



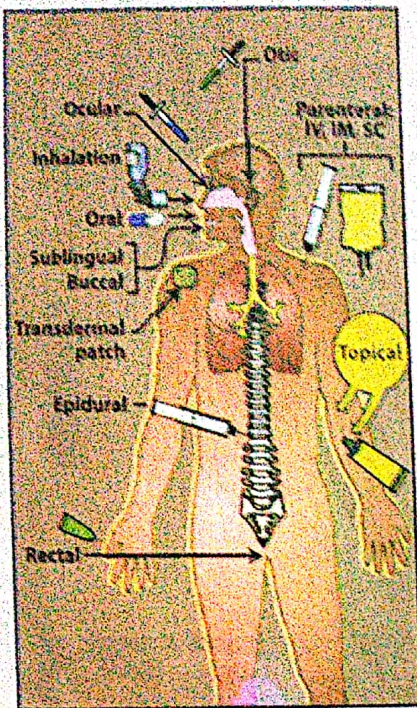


Figure 1.2

Commonly used routes of drug administration. IV = intravenous; IM = intramuscular; SC = subcutaneous.

A. Enteral

Enteral administration (administering a drug by mouth) is the safest and most common, convenient, and economical method of drug administration. The drug may be swallowed, allowing oral delivery, or it may be placed under the tongue (sublingual), or between the gums and cheek (buccal), facilitating direct absorption into the bloodstream.

1. **Oral:** Oral administration provides many advantages. Oral drugs are easily self-administered, and toxicities and/or overdose of oral drugs may be overcome with antidotes, such as activated charcoal. However, the pathways involved in oral drug absorption are the most complicated, and the low gastric pH inactivates some drugs. A wide range of oral preparations is available including enteric-coated and extended-release preparations.

a. **Enteric-coated preparations:** An enteric coating is a chemical envelope that protects the drug from stomach acid, delivering it instead to the less acidic intestine, where the coating dissolves and releases the drug. Enteric coating is useful for certain drugs (for example, *omeprazole*) that are acid unstable. Drugs that are irritating to the stomach, such as *aspirin*, can be formulated with an enteric coating that only dissolves in the small intestine, thereby protecting the stomach.

b. **Extended-release preparations:** Extended-release (abbreviated ER or XR) medications have special coatings or ingredients that control the drug release, thereby allowing for slower absorption and a prolonged duration of action. ER formulations can be dosed less frequently and may improve patient compliance. Additionally, ER formulations may maintain concentrations within the therapeutic range over a longer period of time, as opposed to immediate-release dosage forms, which may result in larger peaks and troughs in plasma concentration. ER formulations are advantageous for drugs with short half-lives. For example, the half-life of oral *morphine* is 2 to 4 hours, and it must be administered six times daily to provide continuous pain relief. However, only two doses are needed when extended-release tablets are used. Unfortunately, many ER formulations have been developed solely for a marketing advantage over immediate-release products, rather than a documented clinical advantage.

2. **Sublingual/buccal:** Placement under the tongue allows a drug to diffuse into the capillary network and enter the systemic circulation directly. Sublingual administration has several advantages, including ease of administration, rapid absorption, bypass of the harsh gastrointestinal (GI) environment, and avoidance of first-pass metabolism (see discussion of first-pass metabolism below). The buccal route (between the cheek and gum) is similar to the sublingual route.

B. Parenteral

The parenteral route introduces drugs directly into the systemic circulation. Parenteral administration is used for drugs that are poorly

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II. Routes of Drug Administration

absorbed from the GI tract (for example, insulin) or injected in the GI tract (for example, insulin). Parenteral administration is used if a patient is unable to take oral medications (debilitated patients) and in circumstances that require a rapid onset of action. In addition, parenteral routes have the highest bioavailability and are not subject to first-pass metabolism of the drug. Parenteral administration provides the most control over the actual dose of drug delivered to the body. However, these routes of administration are irreversible and may cause pain, local tissue damage, and infections. The three major parenteral routes are intravascular (intravenous or intra-arterial), intrafascicular, and subcutaneous (Figure 1.3).

- 1. Intravenous (IV):** IV injection is the most common parenteral route. It is useful for drugs that are not absorbed orally, such as the neuromuscular blocker rocuronium. IV delivery permits a rapid effect and a maximum degree of control over the amount of drug delivered. When injected as a bolus, the full amount of drug is delivered to the systemic circulation almost immediately. If administered as an IV infusion, the drug is infused over a longer period of time, resulting in lower peak plasma concentrations and an increased duration of circulating drug levels. IV administration is advantageous for drugs that cause irritation when administered via other routes, because the substance is rapidly diluted by the blood. Unlike drugs given orally, those that are injected cannot be recalled by strategies such as binding to activated charcoal. IV injection may inadvertently introduce infections through contamination at the site of injection. It may also precipitate blood constituents, induce hemolysis, or cause other adverse reactions if the medication is delivered too rapidly and high concentrations are reached too quickly. Therefore, patients must be carefully monitored for drug reactions, and the rate of infusion must be carefully controlled.
- 2. Intramuscular (IM):** Drugs administered IM can be in aqueous solutions, which are absorbed rapidly, or in specialized depot preparations, which are absorbed slowly. Depot preparations often consist of a suspension of the drug in a nonaqueous vehicle such as polyethylene glycol. As the vehicle diffuses out of the muscle, the drug precipitates at the site of injection. The drug then dissolves slowly, providing a sustained dose over an extended period of time. Examples of sustained-release drugs are haloperidol (see Chapter 11) and depot medroxyprogesterone (see Chapter 26).
- 3. Subcutaneous (SC):** Like IM injection, SC injection provides absorption via simple diffusion and is slower than the IV route. SC injection minimizes the risks of hemolysis or thrombosis associated with IV injection and may provide constant, slow, and sustained effects. This route should not be used with drugs that cause tissue irritation, because severe pain and necrosis may occur. Drugs commonly administered via the subcutaneous route include insulin and heparin.



Figure 1.3
A. Schematic representation of subcutaneous and intramuscular injection. B. Plasma concentrations of midazolam after intravenous and intramuscular injection.

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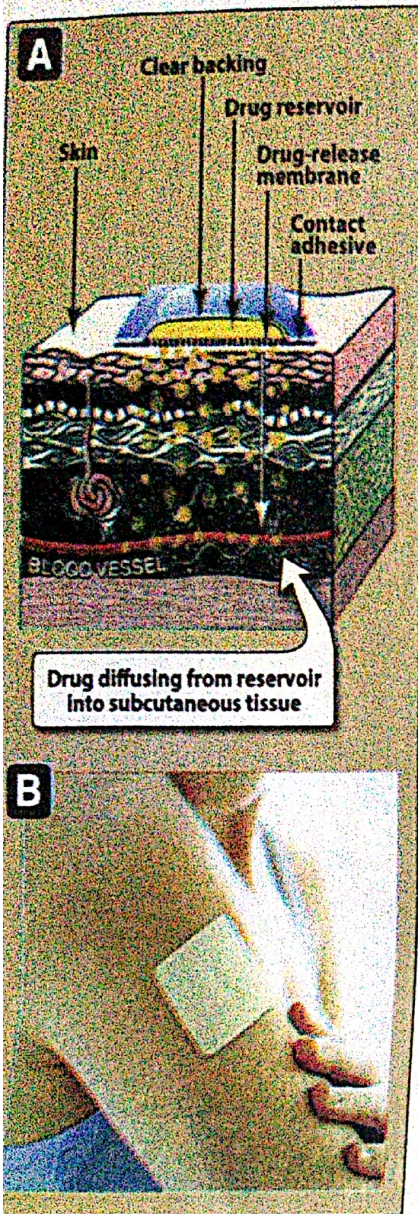


Figure 1.4

Schematic representation of a transdermal patch. B. Transdermal nicotine patch applied to the arm.

C. Other

- 1. Oral inhalation:** Inhalation routes, both oral and nasal (see discussion of nasal inhalation), provide rapid delivery of a drug across the large surface area of the mucous membranes of the respiratory tract and pulmonary epithelium. Drug effects are almost as rapid as those with IV bolus. Drugs that are gases (for example, some anesthetics) and those that can be dispersed in an aerosol are administered via inhalation. This route is effective and convenient for patients with respiratory disorders (such as asthma or chronic obstructive pulmonary disease), because the drug is delivered directly to the site of action, thereby minimizing systemic side effects. Examples of drugs administered via inhalation include bronchodilators, such as albuterol, and corticosteroids, such as fluticasone.
- 2. Nasal inhalation:** This route involves administration of drugs directly into the nose. Examples of agents include nasal decongestants, such as oxymetazoline, and corticosteroids, such as mometasone furoate. Desmopressin is administered intranasally in the treatment of diabetes insipidus.
- 3. Intrathecal/Intraventricular:** The blood-brain barrier typically delays or prevents the absorption of drugs into the central nervous system (CNS). When local, rapid effects are needed, it is necessary to introduce drugs directly into the cerebrospinal fluid. For example, intrathecal amphotericin B is used in treating cryptococcal meningitis (see Chapter 42).
- 4. Topical:** Topical application is used when a local effect of the drug is desired. For example, clotrimazole is a cream applied directly to the skin for the treatment of fungal infections.
- 5. Transdermal:** This route of administration achieves systemic effects by application of drugs to the skin, usually via a transdermal patch (Figure 1.4). The rate of absorption can vary markedly, depending on the physical characteristics of the skin at the site of application, as well as the lipid solubility of the drug. This route is most often used for the sustained delivery of drugs, such as the antianginal drug nitroglycerin, the antiemetic scopolamine, and nicotine transdermal patches, which are used to facilitate smoking cessation.
- 6. Rectal:** Because 50% of the drainage of the rectal region bypasses the portal circulation, the biotransformation of drugs by the liver is minimized with rectal administration. The rectal route has the additional advantage of preventing destruction of the drug in the GI environment. This route is also useful if the drug induces vomiting when given orally, if the patient is already vomiting, or if the patient is unconscious. [Note: The rectal route is commonly used to administer antiemetic agents] Rectal absorption is often erratic and incomplete, and many drugs irritate the rectal mucosa. Figure 1.5 summarizes the characteristics of the common routes of administration.