Pharmacokinetic Principles

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ADME

- **A**bsorption
- **D**istribution
- **M**etabolism
- **E**xcretion

Pharmacokinetic parameters

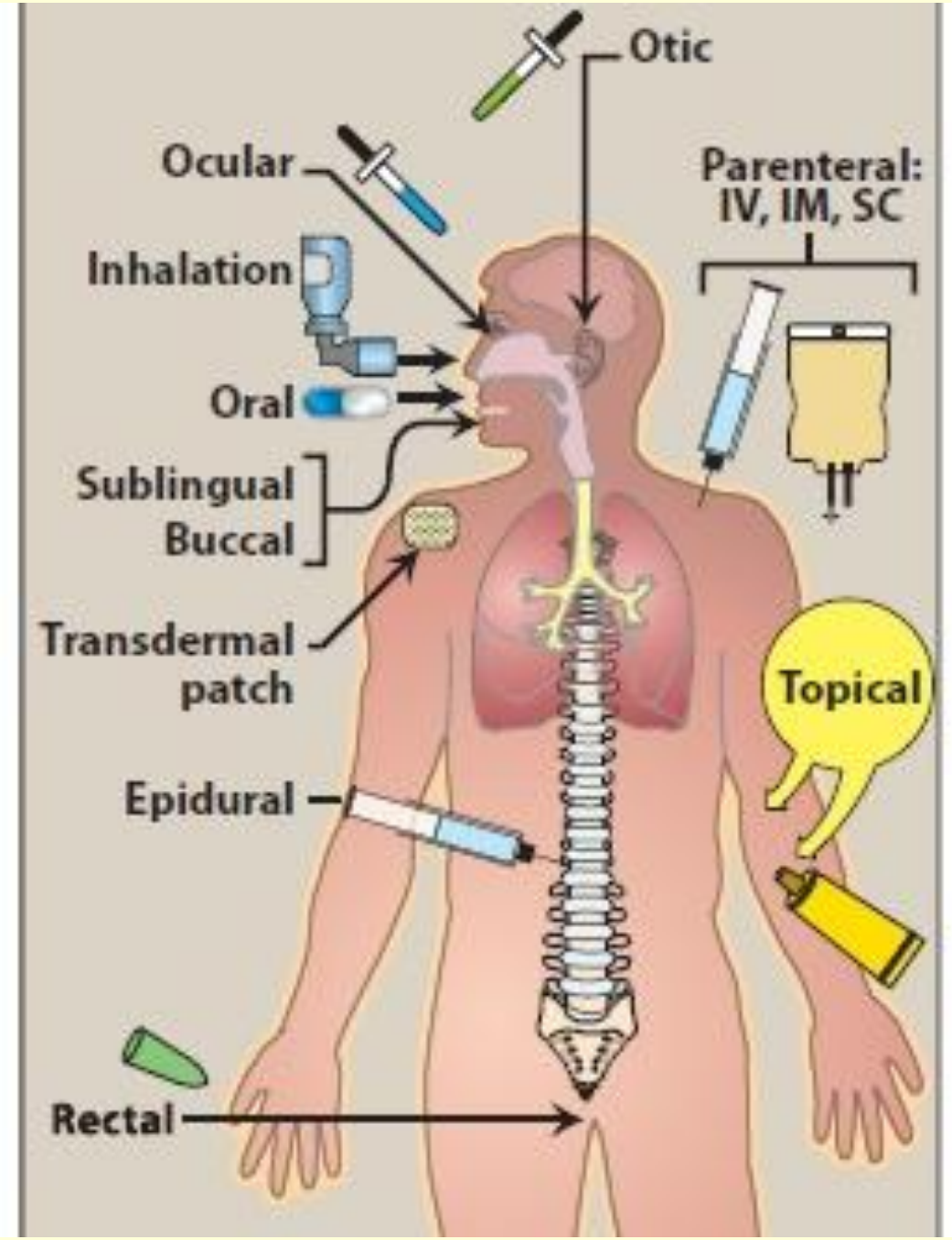
- **Absorption:** First, absorption from the site of administration permits entry of the drug (either directly or indirectly) into plasma.
- **Distribution:** Second, the drug may then reversibly leave the bloodstream and distribute into the interstitial and intracellular fluids.
- **Metabolism:** Third, 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.

Pharmacokinetic parameters

Important for clinicians to design optimal drug regimens, including:

- the route of administration,
- the dose, the frequency,
- the duration of treatment.

Routes of Drug Administration



Routes of Drug Administration

A. Enteral administration (by mouth)

1. **Oral administration.**

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.

a. **Extended-release preparations:** medications have special coatings or ingredients that control the drug release, thereby allowing for slower absorption and a prolonged duration of action.

2. **Sublingual/buccal:** Placement under the tongue allows a drug to diffuse into the capillary network and enter the systemic circulation directly.

Routes of Drug Administration

B. Parentral administration:
Introduces drug directly into the systemic circulation

1. **Intravenous (IV):** it is the most common and it is useful for drugs that are not absorbed orally. IV delivery permits a rapid effect and a maximum degree of control over the amount of drug delivered.

   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.

Routes of Drug Administration

B. Parentral administration:
Introduces drug directly into the systemic circulation

2. **Intramuscular (IM):** Drugs administered IM can be in aqueous solutions, 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.

3. **Subcutaneous (SC):** Like IM injection, SC injection provides absorption via simple diffusion and is slower than the IV route.

Routes of Drug Administration

C. Other routs:

1. **Oral inhalation:** Inhalation routes, both oral and nasal 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.

2. **Nasal inhalation:** This route involves administration of drugs directly into the nose. Examples of agents include nasal decongestants, e.g. **oxymetazoline**, and **mometasone.** Also, **Desmopressin** is administered intranasally in the treatment of diabetes insipidus.

Routes of Drug Administration

C. Other routs:

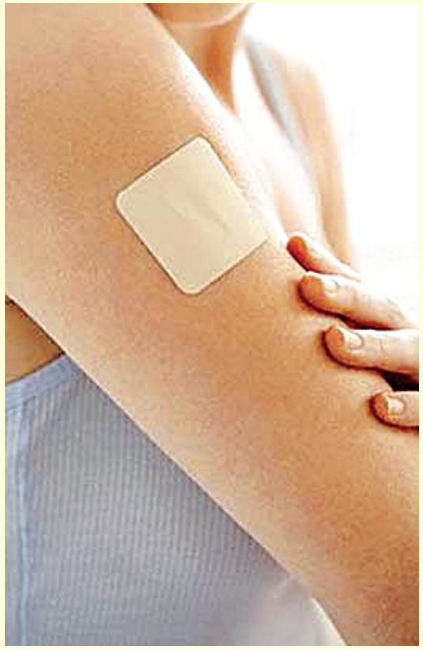
3. **Intrathecal/ intraventricular:** The blood–brain barrier typically delays or prevents the absorption of drugs into the central nervous system (CNS). When local, rapid effects are needed, it is necessary to introduce drugs directly into the cerebrospinal fluid. For example, intrathecal **amphotericin B** is used in treating cryptococcal meningitis.

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.

Routes of Drug Administration

C. Other routs:

5. **Transdermal:** This route of administration achieves systemic effects by application of drugs to the skin, usually via a transdermal patch. 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.



The absorption pattern, advantages, and disadvantages of the most common routes of administration.

Route of administration	Absorption Pattern	advantages	disadvantages
Oral	Variable; affected by many factors	Safest and most common, convenient, and economical route of administration	Limited absorption of some drugs, Food may affect absorption, needs Patient compliance, Drugs metabolized before absorption
Intravenous **I.V.**	Absorption not required	Immediate effects, Ideal for large volumes, Suitable for irritating substances and complex mixtures, helpful in emergency, Dosage titration permissible, Ideal for high molecular weight proteins and peptides.	Unsuitable for oily substances, Bolus injection may result in adverse effects, Most substances must be slowly Injected, Strict aseptic techniques needed.
Subcutaneous **S.C.**	Depends on drug diluents: Aqueous solution: prompt Depot preparations: slow and sustained	Suitable for slow-release drugs, Ideal for some poorly soluble suspensions	Pain or necrosis if drug is irritating, Unsuitable for drugs administered in large volumes

The absorption pattern, advantages, and disadvantages of the most common routes of administration.

Route of administration	Absorption Pattern	advantages	disadvantages
Intramuscular **I.M.**	Depends on diluents Aqueous solution: prompt, Depot preparations: slow and sustained	Suitable if drug volume is moderate, Suitable for oily vehicles and certain irritating substances, Preferable to intravenous if patient must self-administer.	Affects certain lab tests (creatine kinase), Can be painful, Can cause intramuscular hemorrhage (precluded during anticoagulation therapy)
Transdermal (patch)	Slow and sustained	Bypasses the first-pass effect, Convenient and painless, Ideal for drugs that are lipophilic and have poor oral bioavailability, Ideal for drugs that are quickly eliminated from the body	Some patients are allergic to patches, causes irritation, Drug must be highly lipophilic, May cause delayed delivery of drug to site of action, Limited to drugs that can be taken in small daily doses
Rectal	Erratic and variable	Partially bypasses first-pass effect, Bypasses destruction by stomach acid, Ideal if drug causes vomiting, Ideal in patients who are vomiting, or comatose	Drugs may irritate the rectal mucosa, Not a well-accepted route

The absorption pattern, advantages, and disadvantages of the most common routes of administration.

Route of administration	Absorption Pattern	advantages	disadvantages
Inhalation	Systemic absorption may occur; this is not always desirable	Absorption is rapid; can have immediate effects, Ideal for gases, Eective for patients with respiratory problems, Dose can be titrated, Localized effect to target lungs: lower doses used compared to that with oral or parenteral administration, Fewer systemic side effects	Most addictive route (drug can enter the brain quickly), Patient may have difficulty regulating dose, Some patients may have difficulty using inhalers
Sublingual	Depends on the drug: Few drugs (e.g. nitroglycerin) have rapid, direct systemic absorption, Most drugs incompletely absorbed	Bypasses first-pass effect, Bypasses destruction by stomach acid, Drug stability maintained because the pH of saliva relatively neutral, May cause immediate pharmacological effects	Limited to certain types of drugs, Limited to drugs that can be taken in small doses, May lose part of the drug dose if swallowed

Routes of Drug Administration

C. Other routs:

5. 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.

ABSORPTION OF DRUGS

Absorption: is the transfer of a drug from the site of administration to the bloodstream.

Mechanisms of absorption of drugs from the GI tract:

1. **Passive diffusion:**

- It is a concentration dependent, the drug moves from a region of high concentration to one of lower concentration.
- Cellular energy and carrier are not required.

1. **Facilitated diffusion:** Other agents can enter the cell through specialized transmembrane carrier proteins that facilitate the passage of large molecules.

- It does not require energy,
- can be saturated
- may be inhibited by compounds that compete for the carrier.

ABSORPTION OF DRUGS

Mechanisms of absorption of drugs from the GI tract:

3. **Active transport:** A few drugs that closely resemble the structure of naturally occurring metabolites (endogenous molecules) are actively transported across cell membranes using specific carrier proteins.

- Require specific carrier proteins
- Require energy (hydrolysis of adenosine triphosphate)
- moving drugs against a concentration gradient
- can be saturated
- may be inhibited by compounds that compete for the carrier.

ABSORPTION OF DRUGS

Mechanisms of absorption of drugs from the GI tract:

4. Endocytosis and exocytosis: This type of absorption is used to transport drugs of exceptionally large size across the cell membrane.

Endocytosis involves engulfment of a drug by the cell membrane and transport into the cell by pinching off the drug filled vesicle.

Exocytosis is the reverse of endocytosis. Many cells use exocytosis to secrete substances out of the cell through a similar process of vesicle formation. **Vitamin B12** is transported across the gut wall by endocytosis.

Factors influencing absorption

1. Effect of pH on drug absorption:

Most drugs are either weak acids or weak bases. Acidic drugs (HA) release a proton (H+), causing a charged anion (A−) to form:

$$HA \rightleftharpoons H^+ + A^-$$

Weak bases (BH+) can also release an H+. However, the protonated form of basic drugs is usually charged, and loss of a proton produces the uncharged base (B):

$$BH^+ \rightleftharpoons B + H^+$$

A drug passes through membranes more readily if it is uncharged. Thus, for a weak acid, the uncharged, protonated HA can permeate through membranes, and A− cannot. For a weak base, B penetrates through the cell membrane, but the protonated form BH+ does not.

Factors influencing absorption

2. Blood flow to the absorption site:

The intestines receive much more blood flow than the stomach, so absorption from the intestine is favoured over the stomach.

3. Total surface area available for absorption:

With a surface rich in brush borders containing microvilli, the intestine has a surface area about 1000-fold that of the stomach, making absorption of the drug across the intestine more efficient.

Factors influencing absorption

3. Contact time at the absorption surface:

If a drug moves through the GI tract very quickly, as can happen with severe diarrhea, it is not well absorbed. Also, anything that delays the transport of the drug from the stomach to the intestine delays the rate of absorption of the drug.

4. Expression of P-glycoprotein:

It is a transmembrane transporter protein. It is expressed in tissues throughout the body, including the liver, kidneys, placenta, intestines, and brain capillaries, and is involved in transportation of drugs from tissues to blood. In areas of high expression, P-glycoprotein reduces drug absorption.

Bioavailability

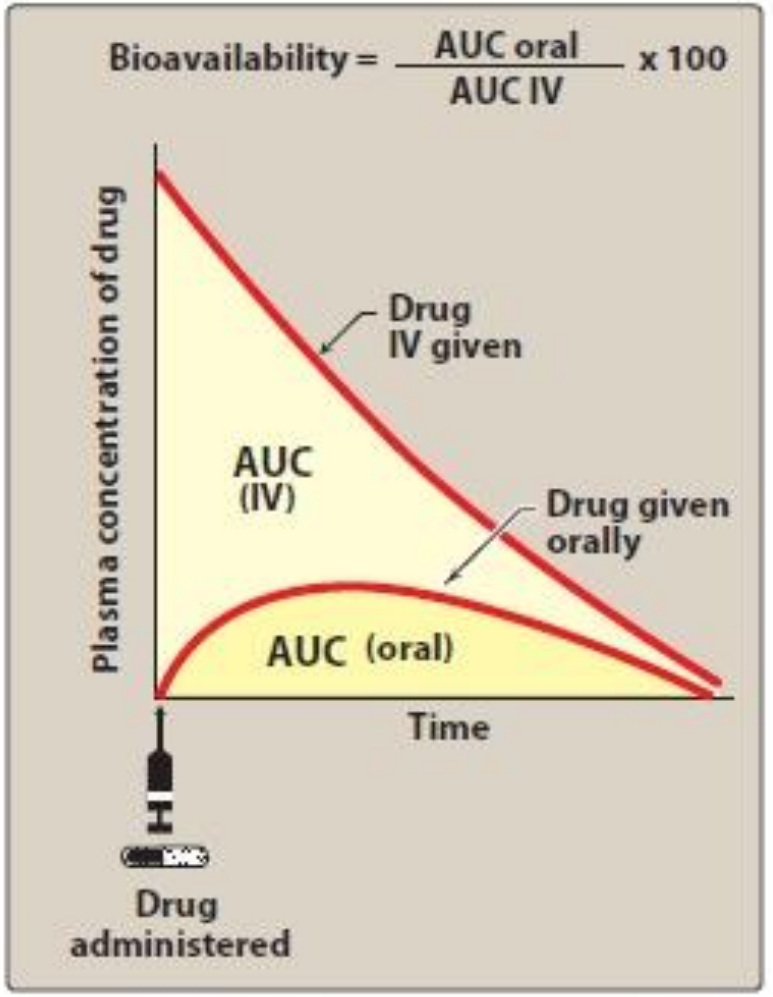
Bioavailability is the rate and extent to which an administered drug reaches the systemic circulation.

For example, if 100 mg of a drug is administered orally and 70 mg is absorbed unchanged, the bioavailability is 0.7 or 70%.

Determining bioavailability is important for calculating drug dosages for non intravenous routes of administration.

Determination of Bioavailability

After IV administration, 100% of the drug rapidly enters the circulation. When the drug is given orally, only part of the administered dose appears in the plasma. By plotting plasma concentrations of the drug versus time, the area under the curve (AUC) can be measured.



Determination of the bioavailability of a drug. AUC = area under curve; IV = intravenous

Importance of Bioavailability

1. Determine the dose and route of administration, e.g.

   Propranolol I.V. 1-10mg, oral 10-320mg (because of First Pass Metabolism).

2. Compare between different formulations of a drug e.g.

   sublingual GTN >90%. oral GTN <10%

3. To know the large number of factors that might increase or decrease the systemic availability of a drug and lead to failure of therapy or to toxicity

   A drug injected I.V. Is 100% available to exert biological effect

Factors influencing Bioavailability

1. First-pass hepatic metabolism:

When a drug is absorbed from the GI tract, it enters the portal circulation before entering the systemic circulation. If the drug is rapidly metabolized in the liver or gut wall during this initial passage, the amount of unchanged drug entering the systemic circulation is decreased. First-pass metabolism by the intestine or liver limits the efficacy of many oral medications.

Factors influencing Bioavailability

2. Solubility of Drugs

Very hydrophilic drugs are poorly absorbed and extremely lipophilic are also poorly absorbed. For a drug to be readily absorbed, it must be largely lipophilic, yet have some solubility in aqueous solutions. This is one reason why many drugs are either weak acids or weak bases.

3. Chemical instability:

Some drugs, such as penicillin G, are unstable in the pH of the gastric contents. Others, such as insulin, are destroyed in the GI tract by degradative enzymes.

Factors influencing Bioavailability

4. Nature of the drug formulation:

Drug absorption may be altered by factors unrelated to the chemistry of the drug. For example, particle size, salt form, crystal polymorphism, enteric coatings, and the presence of excipients (such as binders and dispersing agents) can influence the ease of dissolution and, therefore, alter the rate of absorption.

Bioequivalence

Two drug formulations are bioequivalent if they show comparable bioavailability and similar times to achieve peak blood concentrations.

Therapeutic equivalence

Two drug formulations are therapeutically equivalent if they are pharmaceutically equivalent (that is, they have the same dosage form, contain the same active ingredient, and use the same route of administration) with similar clinical and safety profiles.

Therefore, two drugs that are bioequivalent may not be therapeutically equivalent