Pharmacology

Lec. 1

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Pharmacology can be defined as the study of substances that interact with living systems through chemical processes, especially by binding to regulatory molecules and activating or inhibiting normal body processes

The actions of the drug on the body are termed **pharmacodynamic** processes. These properties determine the group in which the drug is classified, and they play the major role in deciding whether that group is appropriate therapy for a particular symptom or disease.

The actions of the body on the drug are called **pharmacokinetic** processes. Pharmacokinetic processes govern the absorption, distribution, and elimination of drugs and are of great practical importance in the choice and administration of a particular drug for a particular patient, eg, a patient with impaired renal function..

Pharmacokinetics

• **Absorption:** First, absorption from the site of administration permits entry of the drug (either directly or indirectly) into plasma.

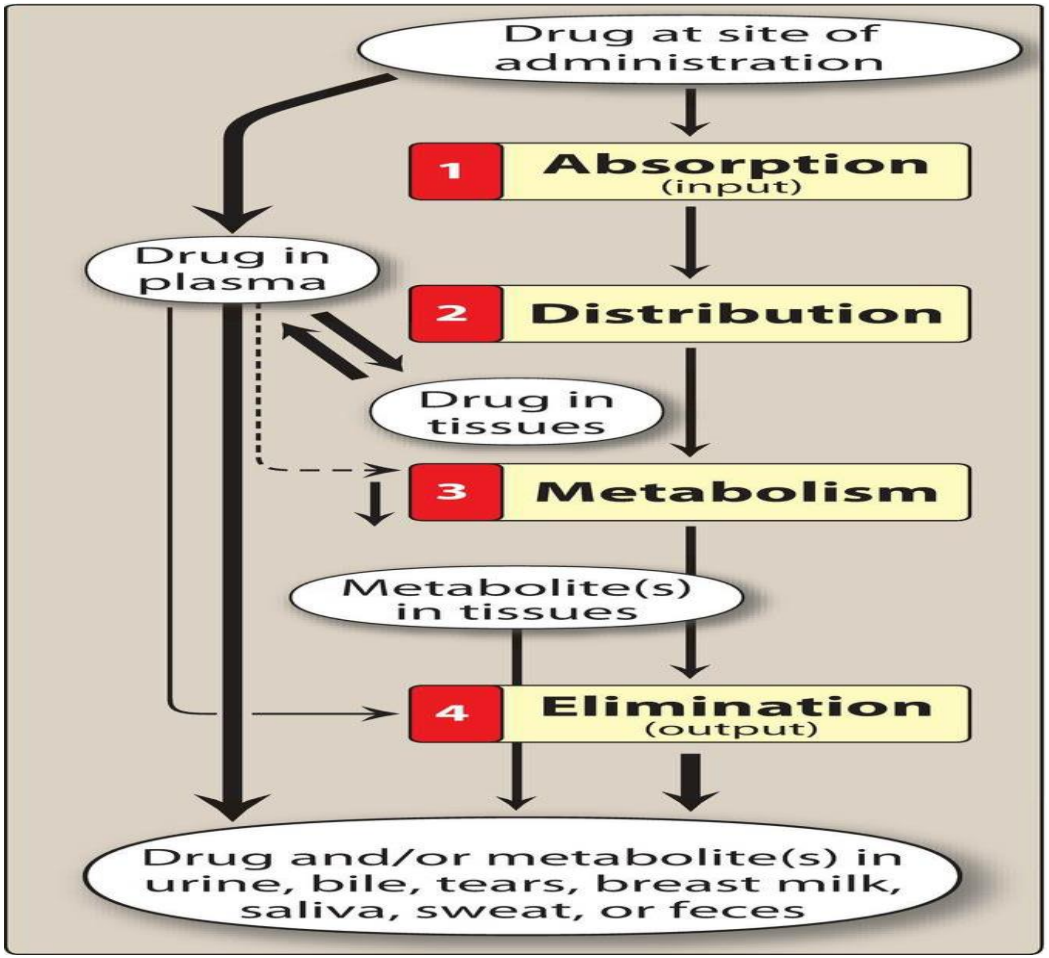
• **Distribution:** Second, the drug may then reversibly leave the bloodstream and distribute into the interstitial and intracellular fluids.

• **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.

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



Routes of drugs administration

The route of administration is determined by properties of the drug and by the therapeutic objectives (for example, the need for 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.

A: 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 blood streem

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 labile, and for drugs that are irritating to the stomach, such as aspirin.

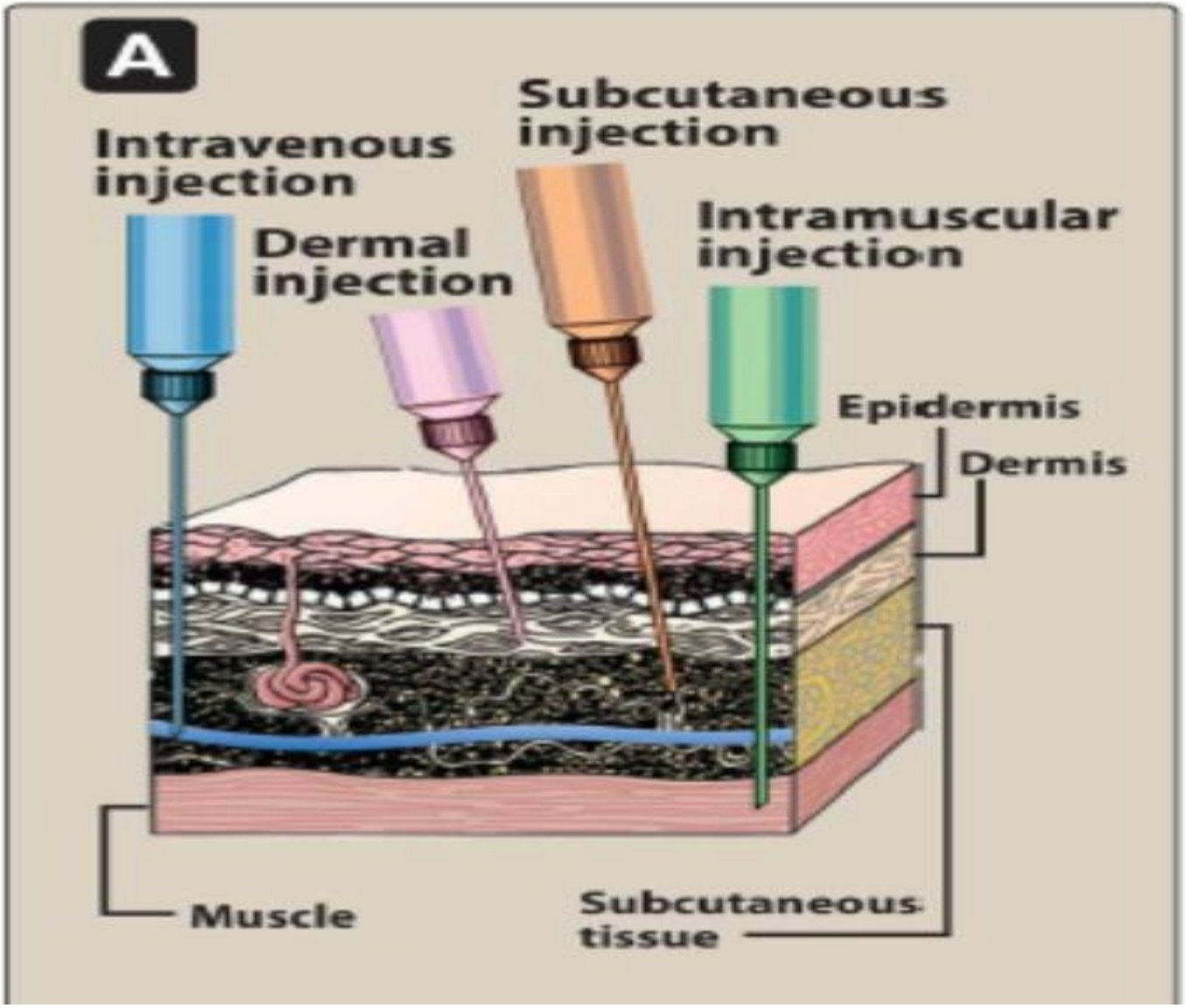
b. Extended-release preparations: Extended-release {abbreviated ER, XR, XL, SR, etc.) medications have special coatings or ingredients that control drug release, thereby allowing for slower absorption and prolonged duration of action. ER formulations can be dosed less frequently and may improve patient compliance. In addition, ER formulations may maintain concentrations within the therapeutic range over a longer duration, 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.

2. Sublingual/buccal: The sublingual route involves placement of drug under the tongue. The buccal route involves placement of drug between the cheek and gum. Both the sublingual and buccal routes of absorption have several advantages, including ease of administration, rapid absorption, bypass of the harsh gastrointestinal (GI) environment, and avoidance of first-pass metabolism

B. Parenteral:

The parenteral route introduces drugs directly into the body by the injection. Parenteral administration is used for drugs that are poorly absorbed from the GI tract (for example, heparin) or unstable in the GI tract (for example, insulin). Parenteral administration is also used if a patient is unable to take oral medications (unconscious 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 or the harsh GI environment. 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, fear, local tissue damage, and infections. The three major parenteral routes are intravascular (intravenous or intra-arterial), intramuscular, and subcutaneous.

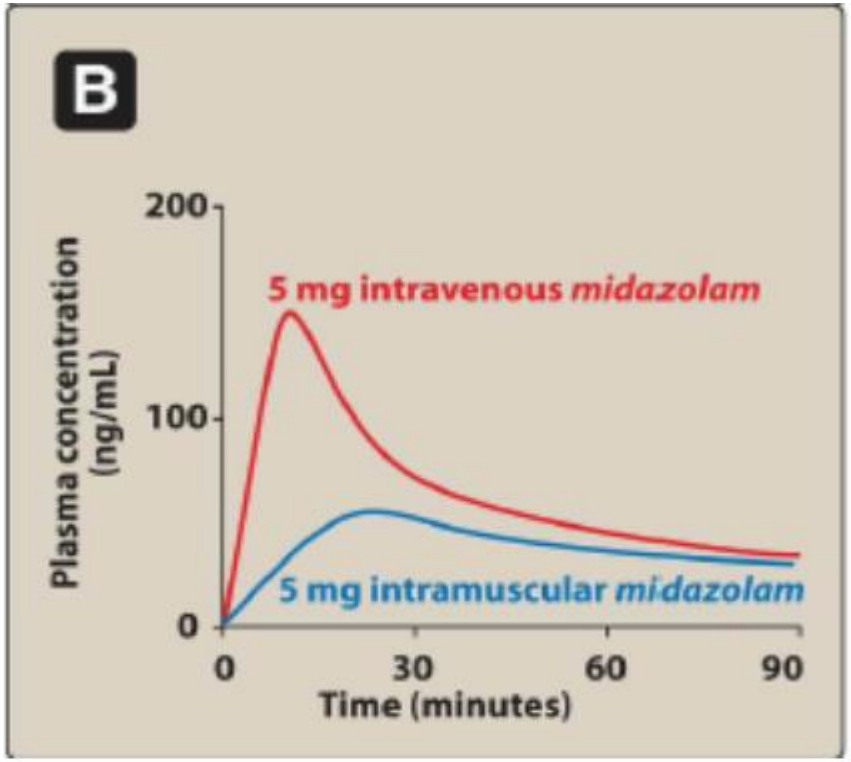
1. Intravenous (IV): IV injection is the most common parenteral route. It is useful for drugs that are not absorbed orally, such as the neuromuscular blocker rocuronium. IV delivery permits a rapid effect and a maximum degree of control over the amount of drug delivered. When injected as a bolus, the 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, resulting in lower peak plasma concentrations and an increased duration of circulating drug.


A
Intravenous injection
Dermal injection
Subcutaneous injection
Intramuscular injection
Epidermis
Dermis
Muscle
Subcutaneous tissue

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 drug in a nonaqueous vehicle, such as polyethylene glycol. As the vehicle diffuses out of the muscle, drug precipitates at the site of injection. The drug then dissolves slowly, providing a sustained dose over an extended interval.

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.

4. Intradermal: The intradermal (I D) route involves injection into the dermis, the more vascular layer of skin under the epidermis. Agents for diagnostic determination and desensitization are usually administered by this route

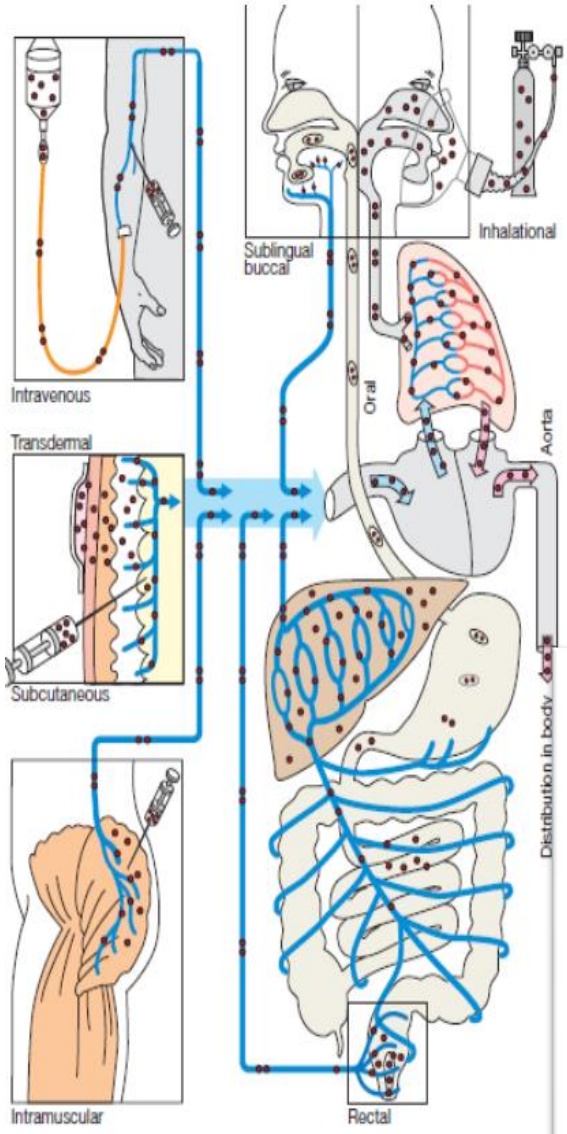


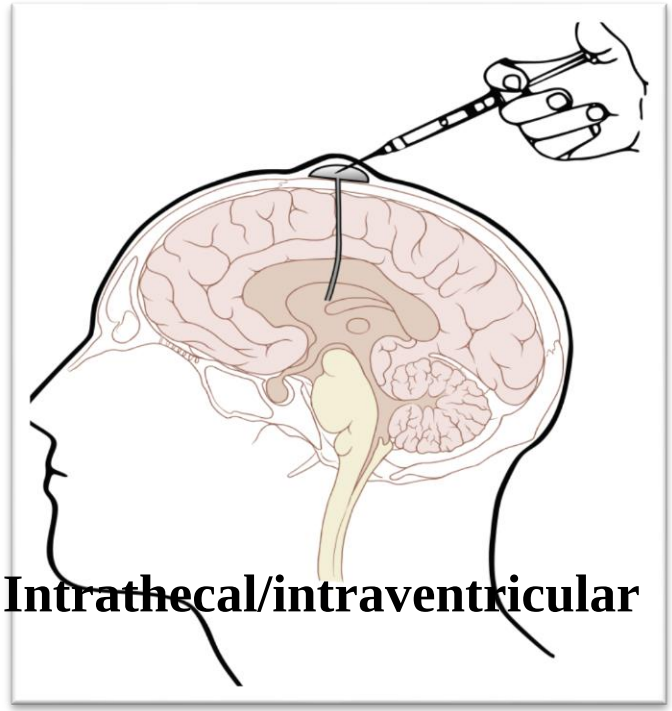
C. Other:

1. Oral inhalation and nasal preparations: Both the oral inhalation and nasal routes of administration provide rapid delivery of drug across the large surface area of mucous membranes of the respiratory tract and pulmonary epithelium. Drug effects are almost as rapid as are 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 drug is delivered directly to the site of action, thereby minimizing systemic side effects. The nasal route involves topical administration of drugs directly into the nose, and it is often used for patients with allergic rhinitis.

2. 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.

3. Topical: Topical application is used when a local effect of the drug is desired.





Intrathecal/intraventricular

BUCCAL ROUTE

ADVANTAGES

- Avoid first pass effect
- Rapid absorption
- Drug stability

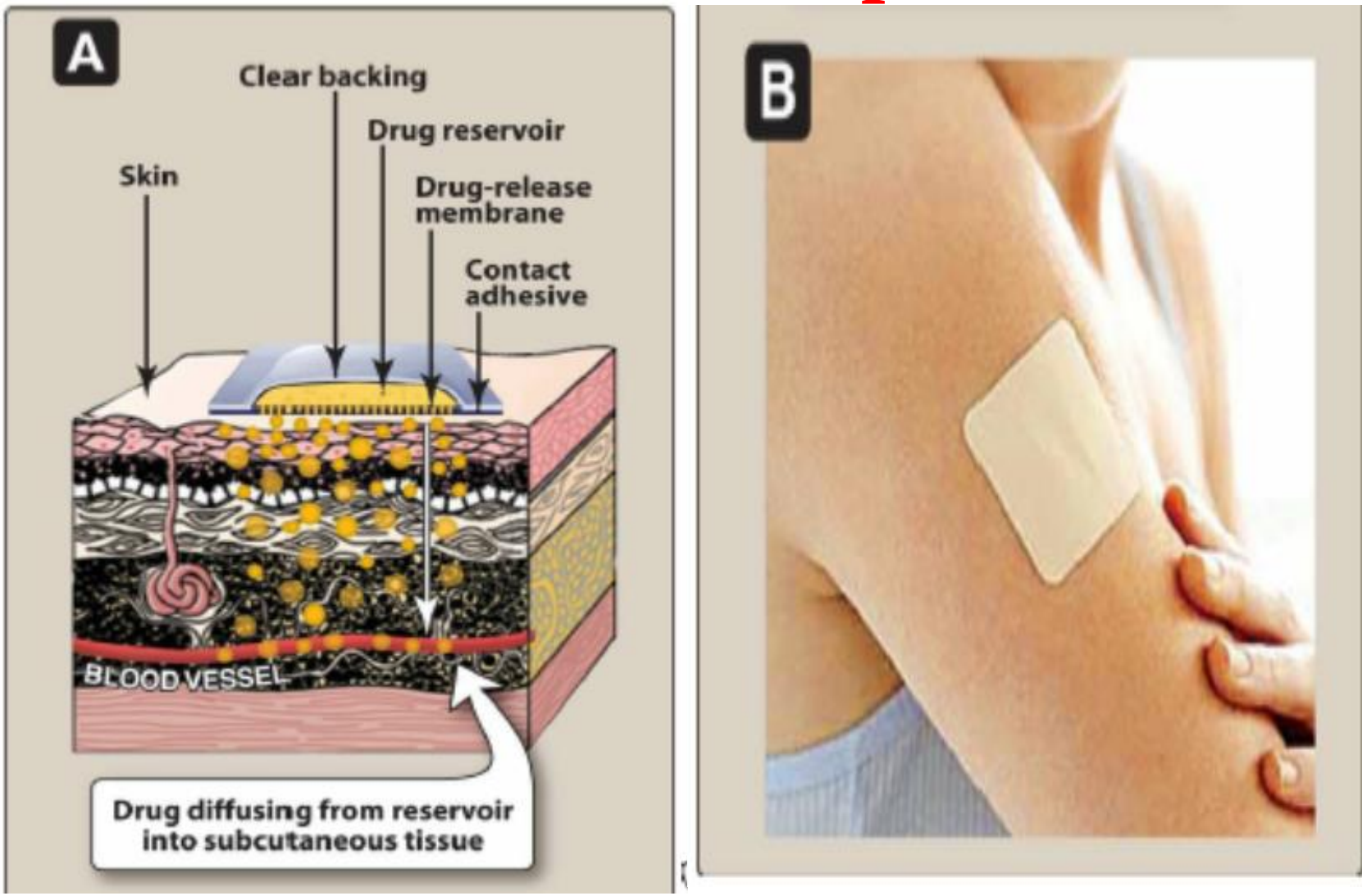
DISADVANTAGES

- Inconvenience
- advantages lost if swallowed
- Small dose limit

4. 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.

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 Gl 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. Rectal absorption is often erratic and incomplete, and many drugs irritate the rectal mucosa. Following figure summarizes characteristics of the common routes of administration, along with example drugs.

Schematic representation of a transdermal patch



ROUTE OF ADMINISTRATION	ABSORPTION PATTERN	ADVANTAGES	DISADVANTAGES	EXAMPLES
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 • Patient compliance is necessary • Drugs may be metabolized before systemic absorption	• *Acetaminophen* tablets • *Amoxicillin* suspension
Sublingual	• Depends on the drug: Few drugs (for example, *nitroglycerin*) have rapid, direct systemic absorption Most drugs erratically or 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	• *Nitroglycerin* • *Buprenorphine*
Intravenous	• Absorption not required	• Can have immediate effects • Ideal if dosed in large volumes • Suitable for irritating substances and complex mixtures • Valuable in emergency situations • Dosage titration permissible • Ideal for high molecular weight proteins and peptide drugs	• Unsuitable for oily substances • Bolus injection may result in adverse effects • Most substances must be slowly injected • Strict aseptic techniques needed	• *Vancomycin* • *Heparin*
Intramuscular	• Depends on drug diluents: Aqueus 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)	• *Haloperidol* • *Depot medroxy-progesterone*

ROUTE OF ADMINISTRATION	ABSORPTION PATTERN	ADVANTAGES	DISADVANTAGES	EXAMPLES
Subcutaneous	• 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	• *Epinephrine* • *Insulin* • *Heparin*
Inhalation	• Systemic absorption may occur; this is not always desirable	• Absorption is rapid; can have immediate effects • Ideal for gases • Effective 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	• *Albuterol* • *Fluticasone*
Topical	• Variable; affected by skin condition, area of skin, and other factors	• Suitable when local effect of drug is desired • May be used for skin, eye, intra-vaginal, and intranasal products • Minimizes systemic absorption • Easy for patient	• Some systemic absorption can occur • Unsuitable for drugs with high molecular weight or poor lipid solubility	• *Clotrimazole* cream • *Hydrocortisone* cream • *Timolol* eye drops
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, which can cause irritation • Drug must be highly lipophilic • May cause delayed delivery of drug to pharmacological site of action • Limited to drugs that can be taken in small daily doses	• *Nitroglycerin* • *Nicotine* • *Scopolamine*
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	• *Bisacodyl* • *Promethazine*

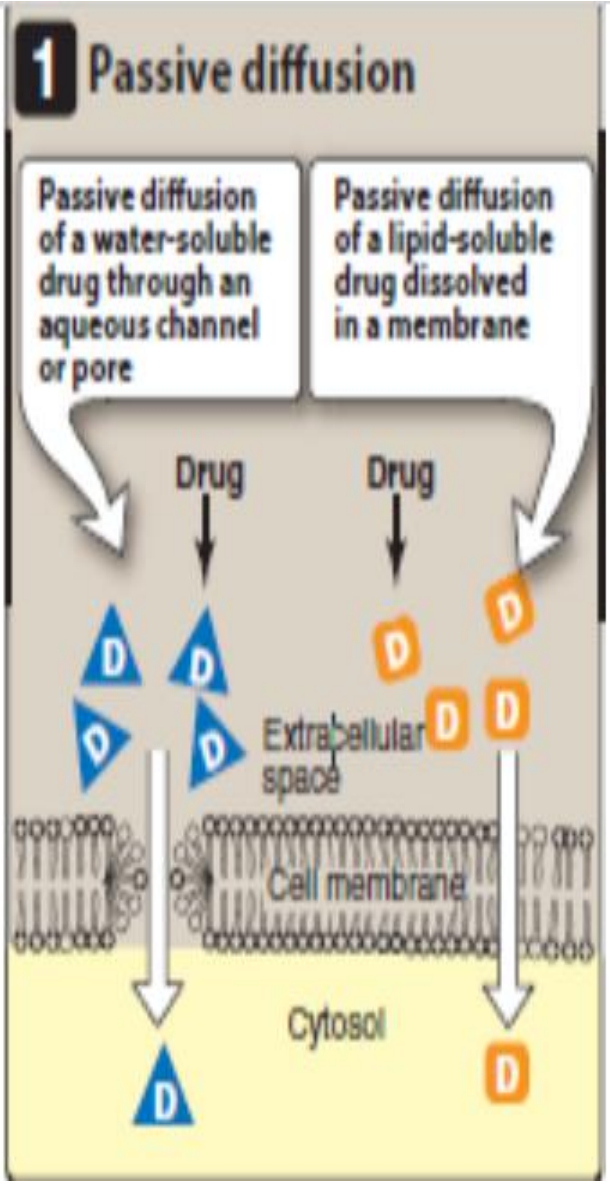
Absorption of drugs:

Absorption is the transfer of a drug from the site of administration to the bloodstream. The rate and extent of absorption depend on the environment where the drug is absorbed, chemical characteristics of the drug, and the route of administration (which influences bioavailability). Routes of administration other than intravenous may result in partial absorption and lower bioavailability.

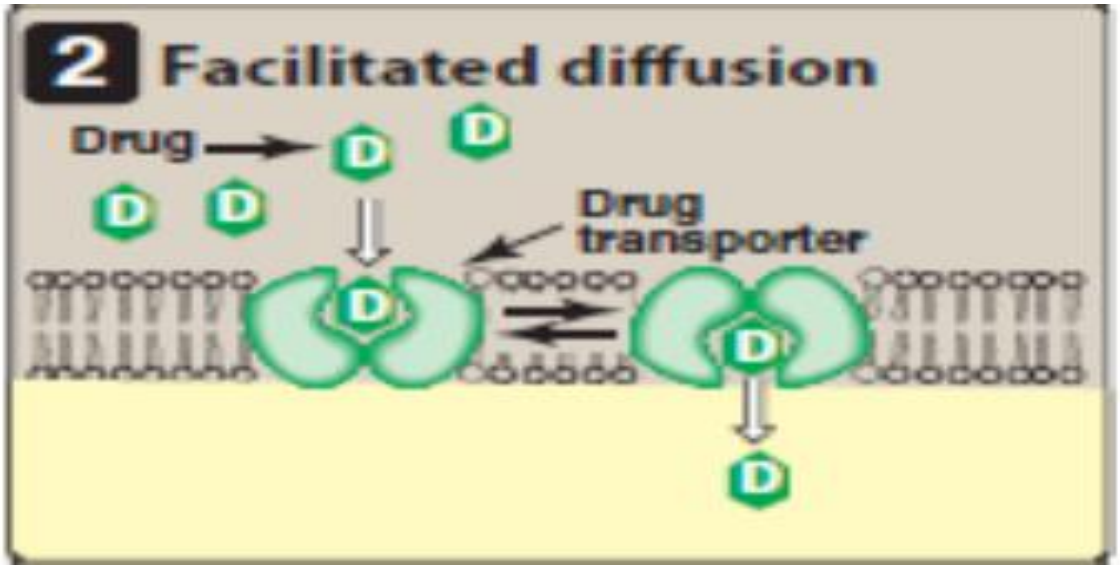
A. Mechanisms of absorption of drugs from the GI tract

Depending on their chemical properties, drugs may be absorbed from the GI tract by passive diffusion, facilitated diffusion, active transport, or endocytosis.

1. Passive diffusion: The driving force for passive diffusion of a drug is the concentration gradient across a membrane separating two body compartments. In other words, the drug moves from an area of high concentration to one of lower concentration. Passive diffusion does not involve a carrier, is not saturable, and shows low structural specificity. The vast majority of drugs are absorbed by this mechanism. Water-soluble drugs penetrate the cell membrane through aqueous channels or pores, whereas lipid-soluble drugs readily move across most biologic membranes due to solubility in the membrane lipid bilayers.

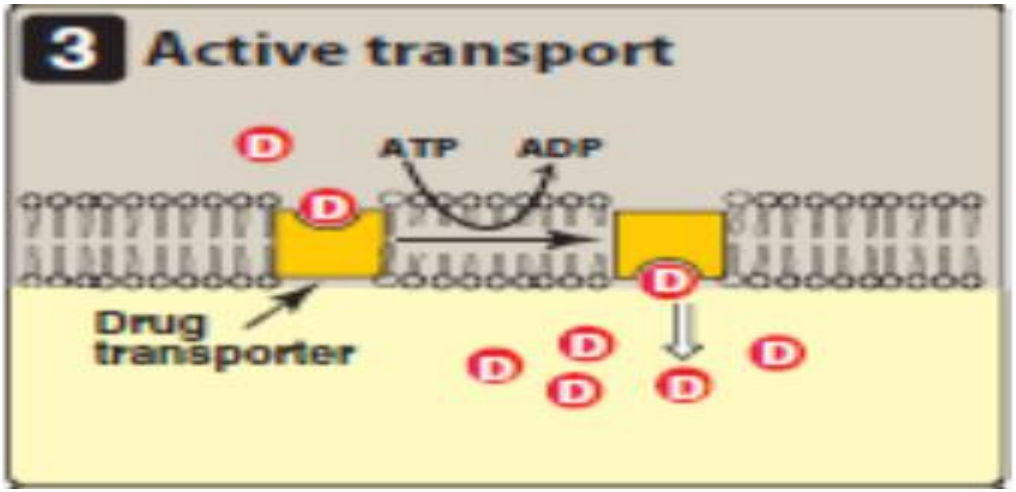


2. Facilitated diffusion: Other agents can enter the cell through specialized transmembrane carrier proteins that facilitate the passage of large molecules. These carrier proteins undergo conformational changes, allowing the passage of drugs or endogenous molecules into the interior of cells. This process is known as facilitated diffusion. It does not require energy, can be saturated, and may be inhibited by compounds that compete for the carrier.

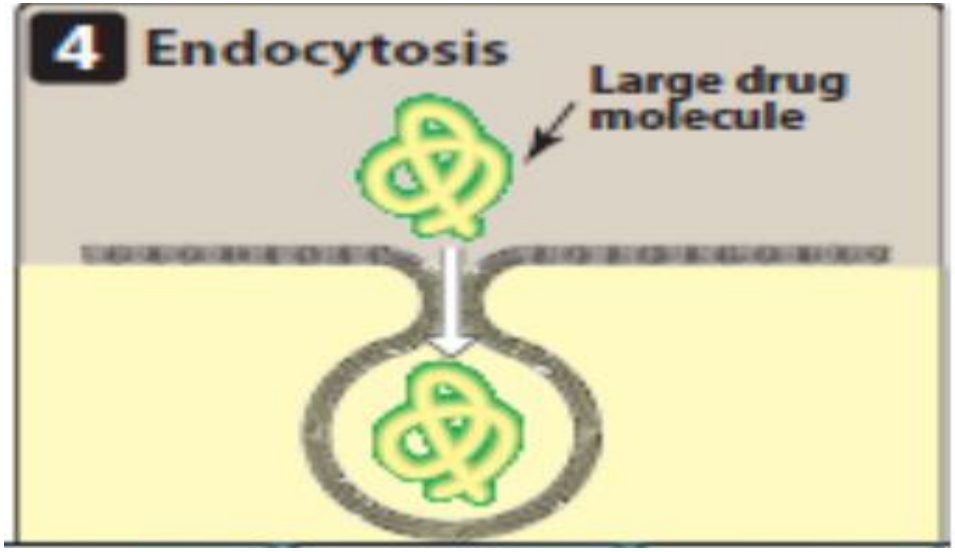


3. Active transport: This mode of drug entry also involves specific carrier proteins that span the membrane. However, active transport is energy dependent, driven by the hydrolysis of adenosine triphosphate (ATP). It is capable of moving drugs against a concentration gradient, from a region of low drug concentration to one of higher concentration. The process is saturable. Active transport

systems are selective and may be competitively inhibited by other co-transported substances.



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, whereas certain neurotransmitters (for example, norepinephrine) are stored in intracellular vesicles in the nerve terminal and released by exocytosis.



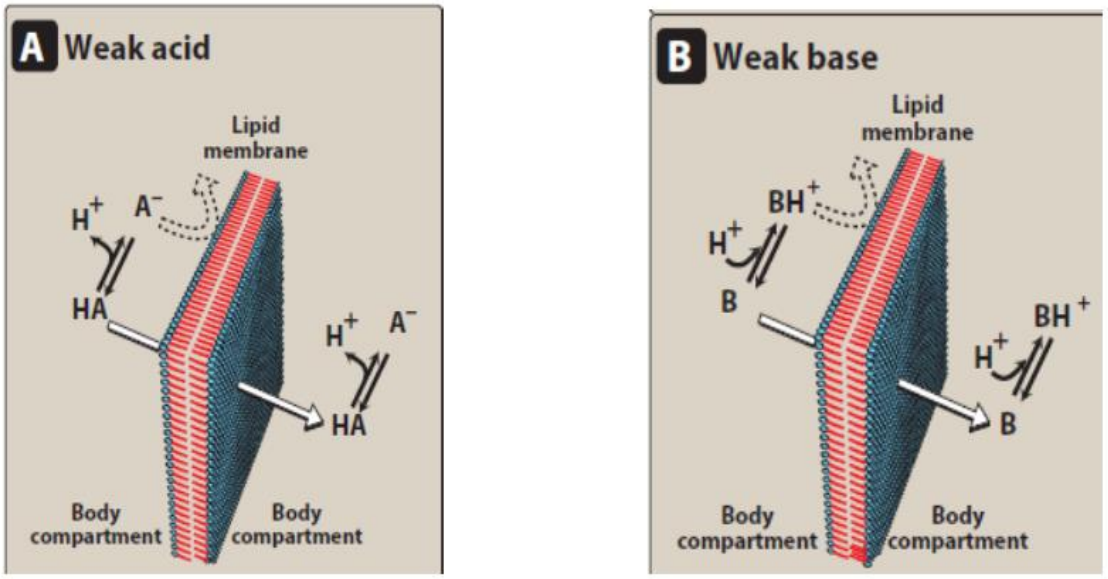
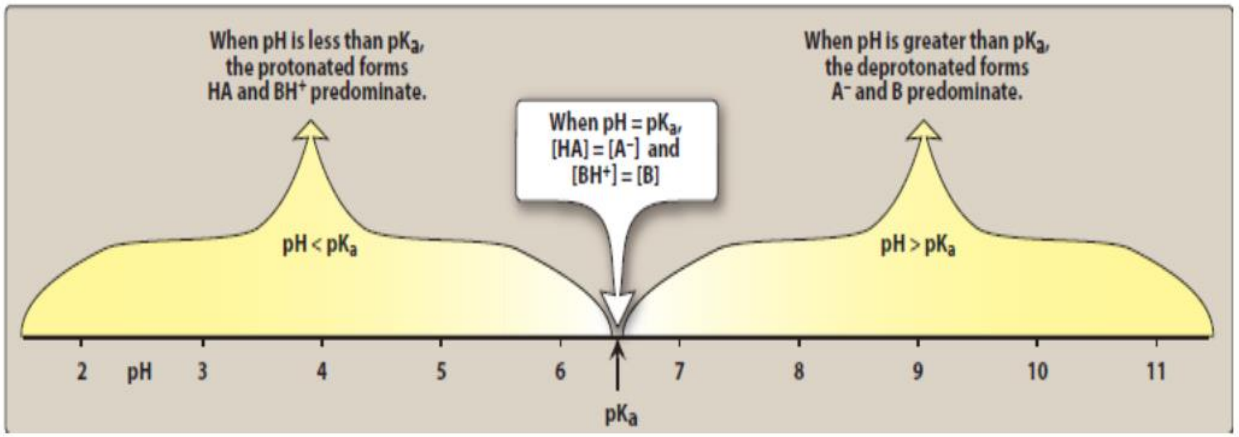


Figure: A. Diffusion of the nonionized form of a weak acid through a lipid membrane. B. Diffusion of the nonionized form of a weak base through a lipid membrane



B. Factors influencing absorption

1. Effect of pH on drug absorption:

Acidic drugs (HA) release a proton (H+), causing a charged anion (A−) to form:

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

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):

$$BH^+ \leftrightarrows B + H^+$$

Most drugs are either weak acids or weak bases. 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, the uncharged form B penetrates through the cell membrane, but the protonated form BH+ does not. Therefore, the effective concentration of the permeable form of each drug at its absorption site is determined by the relative concentrations of the charged and uncharged forms. The ratio between the two forms is, in turn, determined by the pH at the site of absorption and by the strength of the weak acid or base, which is represented by the ionization constant, pKa.

2. Blood flow to the absorption site: The intestines receive much more blood flow than the stomach, so absorption from the intestine is favored 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.

4. 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. Conversely, anything that delays the transport of the drug from the stomach to the intestine delays the rate of absorption of the drug.

5. Expression of P-glycoprotein:

P-glycoprotein is a trans-membrane transporter protein responsible for transporting various molecules, including drugs, across cell membranes.

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. That is, it "pumps" drugs out of the cells. Thus, in areas of high expression, P-glycoprotein reduces drug absorption. In addition to transporting many drugs out of cells, it is also associated with multidrug resistance.

C. 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 70mg is absorbed unchanged, the bioavailability is 0.7 or 70%. Determining bioavailability is important for calculating drug dosages for non-intravenous routes of administration.

1. Determination of bioavailability: Bioavailability is determined by comparing plasma levels of a drug after a particular route of administration (for example, oral administration) with levels achieved by IV administration. 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.

2. Factors that influence bioavailability: In contrast to IV administration, which confers 100% bioavailability, orally administered drugs often undergo first-pass metabolism. This biotransformation, in addition to chemical and physical characteristics of the drug, determines the rate and extent to which the agent reaches the systemic circulation.

a. First-pass hepatic metabolism: When a drug is absorbed from the Gl 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. This is referred to as first pass metabolism. [Note: First-pass metabolism by the intestine or liver limits the efficacy of many oral medications. For example, more than 90% of nitroglycerin is cleared during first-pass metabolism. Hence, it is primarily administered via the sublingual, transdermal, or intravenous route.] Drugs with high first-pass metabolism should be given in doses sufficient to ensure that enough active drug reaches the desired site of action.

b. Solubility of the drug: Very hydrophilic drugs are poorly absorbed because of the inability to cross lipid-rich cell membranes. Paradoxically, drugs that are extremely lipophilic are also poorly absorbed, because they are insoluble in aqueous body fluids and, therefore, cannot gain access to the surface of cells. 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.

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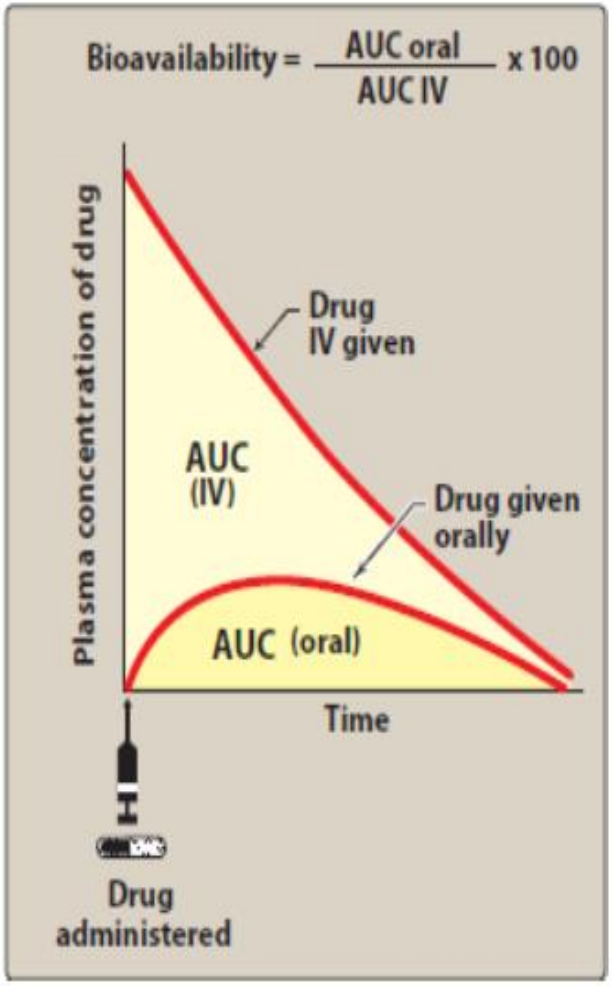
c. Chemical instability: Some drugs, such as penicillin G, are unstable in the pH of gastric contents. Others, such as insulin, are destroyed in the Gl tract by degradative enzymes.

d. 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.

Drug distribution

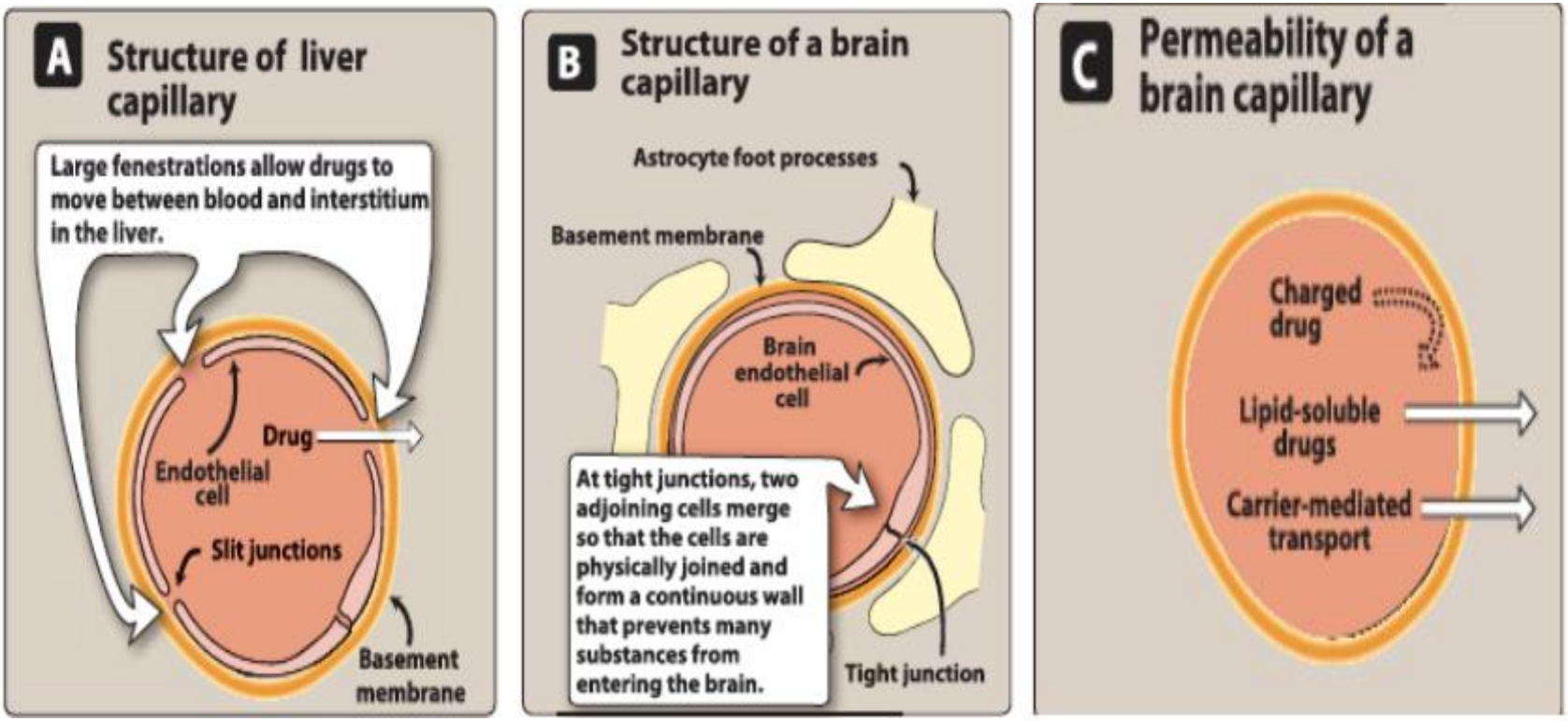
Drug distribution is the process by which a drug reversibly leaves the bloodstream and enters the interstitium (extracellular fluid) and the tissues.

For drugs administered IV, absorption is not a factor, and the initial phase (from immediately after administration through the rapid fall in concentration) represents the distribution phase, during which the drug rapidly leaves the circulation and enters the tissues. The distribution of a drug from the plasma to the interstitium depends on cardiac output and local blood flow, capillary permeability, the tissue volume, the degree of binding of the drug to plasma and tissue proteins, and the relative lipophilicity of the drug.



A. Blood flow

The rate of blood flow to the tissue capillaries varies widely. For instance, blood flow to "vessel-rich organs" (brain, liver, and kidney) is greater than that to the skeletal muscles. Adipose tissue, skin, and viscera have still lower rates of blood flow. Variation in blood flow partly explains the short duration of hypnosis produced by an IV bolus of propofol. High blood flow, together with high lipophilicity of propofol, permits rapid distribution into the CNS and produces anesthesia. A subsequent slower distribution to skeletal muscle and adipose tissue lowers the plasma concentration so that the drug diffuses out of the CNS, down the concentration gradient, and consciousness is regained.


A
Structure of liver capillary
Large fenestrations allow drugs to move between blood and interstitium in the liver.
Drug
Endothelial cell
Slit junctions
Basement membrane
B
Structure of a brain capillary
Astrocyte foot processes
Basement membrane
Brain endothelial cell
At tight junctions, two adjoining cells merge so that the cells are physically joined and form a continuous wall that prevents many substances from entering the brain.
Tight junction
C
Permeability of a brain capillary
Charged drug
Lipid-soluble drugs
Carrier-mediated transport

B. Capillary permeability

Capillary permeability is determined by capillary structure and by the chemical nature of the drug. Capillary structure varies in terms of the fraction of the basement membrane exposed by slit junctions between endothelial cells. In the liver and spleen, a significant portion of the basement membrane is exposed due to large, discontinuous capillaries through which large plasma proteins can pass.

In the brain, the capillary structure is continuous, and there are no slit junctions. To enter the brain, drugs must pass through the endothelial cells of the CNS capillaries or undergo active transport. For example, a specific transporter carries levodopa into the brain. Lipid soluble drugs readily penetrate the CNS because they dissolve in the endothelial cell membrane. By contrast, ionized or polar drugs generally fail to enter the CNS because they cannot pass through the endothelial cells that have no slit junctions. These closely juxtaposed cells form tight junctions that constitute the blood-brain barrier.

C. Binding of drugs to plasma proteins and tissues

1. Binding to plasma proteins: Reversible binding to plasma proteins sequesters drugs in a non-diffusible form and slows transfer out of the vascular compartment. Albumin is the major drug binding protein, and it may act as a drug reservoir. As the concentration of free drug decreases due to elimination, the bound drug dissociates from albumin. This maintains the free-drug concentration as a constant fraction of the total drug in the plasma.

2. Binding to tissue proteins: Many drugs accumulate in tissues, leading to higher concentrations in tissues than in interstitial fluid and blood. Drugs may accumulate because of binding to lipids, proteins, or nucleic acids. Drugs may also undergo active transport into tissues. Tissue reservoirs may serve as a major source of the drug and prolong its actions or cause local drug toxicity. (For example, acrolein, the metabolite of cyclophosphamide, can cause hemorrhagic cystitis because it accumulates in the bladder.)

D. Lipophilicity

The chemical nature of a drug strongly influences its ability to cross cell membranes. Lipophilic drugs readily move across most biologic membranes. These drugs dissolve in the lipid membranes and penetrate the entire cell surface. The major factor influencing the distribution of lipophilic drugs is blood flow to the area. By contrast, hydrophilic drugs do not readily penetrate cell membranes and must pass through slit junctions.

E. Volume of distribution

The apparent volume of distribution, V_d, is defined as the fluid volume that is required to contain the entire drug in the body at the same concentration measured in the plasma. It is calculated by dividing the dose that ultimately gets into the systemic circulation by the plasma concentration at time zero (C_0).

$$V_d = \frac{\text{Amount of drug in the body}}{C_0}$$

Although Vd has no physiologic or physical basis, it can be useful to compare the distribution of a drug with the volumes of the water compartments in the body.

1. Distribution into the water compartments in the body: Once a drug enters the body, it has the potential to distribute into any one of the three functionally distinct compartments of body water or to become sequestered in a cellular site.

a. Plasma compartment: If a drug has a high molecular weight or is extensively protein bound, it is too large to pass through the slit junctions of the capillaries and, thus, is effectively trapped within the plasma (vascular) compartment. As a result, it has a low V_d that approximates the plasma volume, or about 4 L in a 70-kg individual. Heparin shows this type of distribution.

b. Extracellular fluid: If a drug has a low molecular weight but is hydrophilic, it can pass through the endothelial slit junctions of the capillaries into the interstitial fluid. However, hydrophilic drugs cannot move across the lipid membranes of cells to enter the intracellular fluid. Therefore, these drugs distribute into a volume that is the sum of the plasma volume and the interstitial fluid, which together constitute the extracellular fluid (about 20% of body weight or 14L in a 70-kg individual). Aminoglycoside antibiotics show this type of distribution.

c. Total body water: If a drug has a low molecular weight and has enough lipophilicity, it can move into the interstitium through the slit junctions and pass through the cell membranes into the intracellular fluid. These drugs distribute into a volume of about 60% of body weight or about 42 L in a 70-kg individual. Ethanol exhibits this apparent V_d. [Note: In general, a larger V_d indicates greater distribution into tissues; a smaller V_d suggests confinement to plasma or extracellular fluid.]

2. Determination of V_d: The fact that drug clearance is usually a first order process allows calculation of V_d. First order means that a constant fraction of the drug is eliminated per unit of time. This process can be most easily analyzed by plotting the log of the plasma drug concentration (Cp) versus time. The concentration of drug in the plasma can be extrapolated back to time zero (the time of IV bolus) on the Y axis to determine C_0, which is the concentration of drug that would have been

achieved if the distribution phase had occurred instantly. This allows calculation of V_d as:

$$V_d = \frac{\text{Dose}}{C_0}$$

For example, if 10 mg of drug is injected into a patient and the plasma concentration is extrapolated back to time zero, and C_0 = 1 mg/L, then V_d = 10 mg/1 mg/L = 10 L.

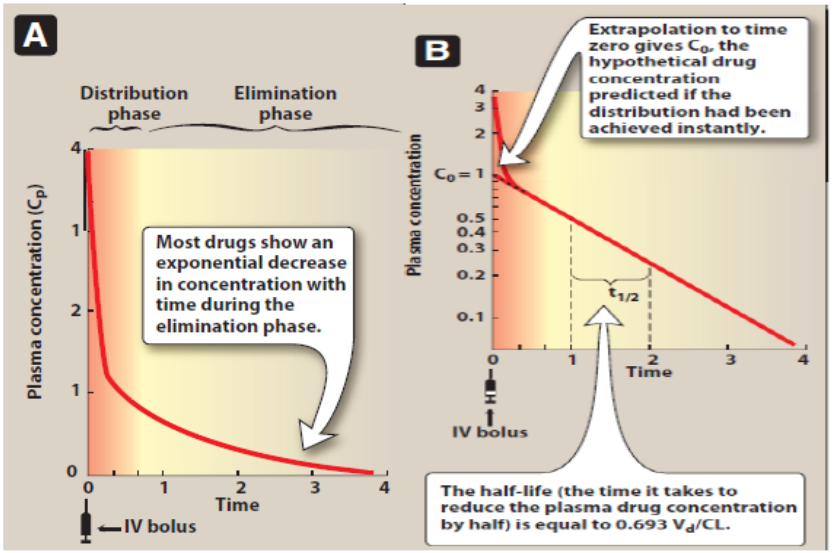


Figure: Drug concentrations in plasma after a single injection of drug at time = 0.

A. Concentration data are plotted on a linear scale. B. Concentration data are plotted on a log scale.

Drug clearance through metabolism:

Once a drug enters the body, the process of elimination begins. The three major routes of elimination are hepatic metabolism, biliary elimination, and urinary elimination. Together, these elimination processes decrease the plasma concentration exponentially. That is, a constant fraction of the drug present is eliminated in a given unit of time.

Most drugs are eliminated according to first-order kinetics, although some, such as *aspirin* in high doses, are eliminated according to zero-order or nonlinear kinetics. Metabolism leads to production of products with increased polarity, which allows the drug to be eliminated. Clearance (CL) estimates the amount of drug cleared from the body per unit of time.

The kidney cannot efficiently eliminate lipophilic drugs that readily cross cell membranes and are reabsorbed in the distal convoluted tubules. Therefore, lipid-soluble agents are first metabolized into more polar (hydrophilic) substances in the liver via two general sets of reactions, called phase I and phase II.

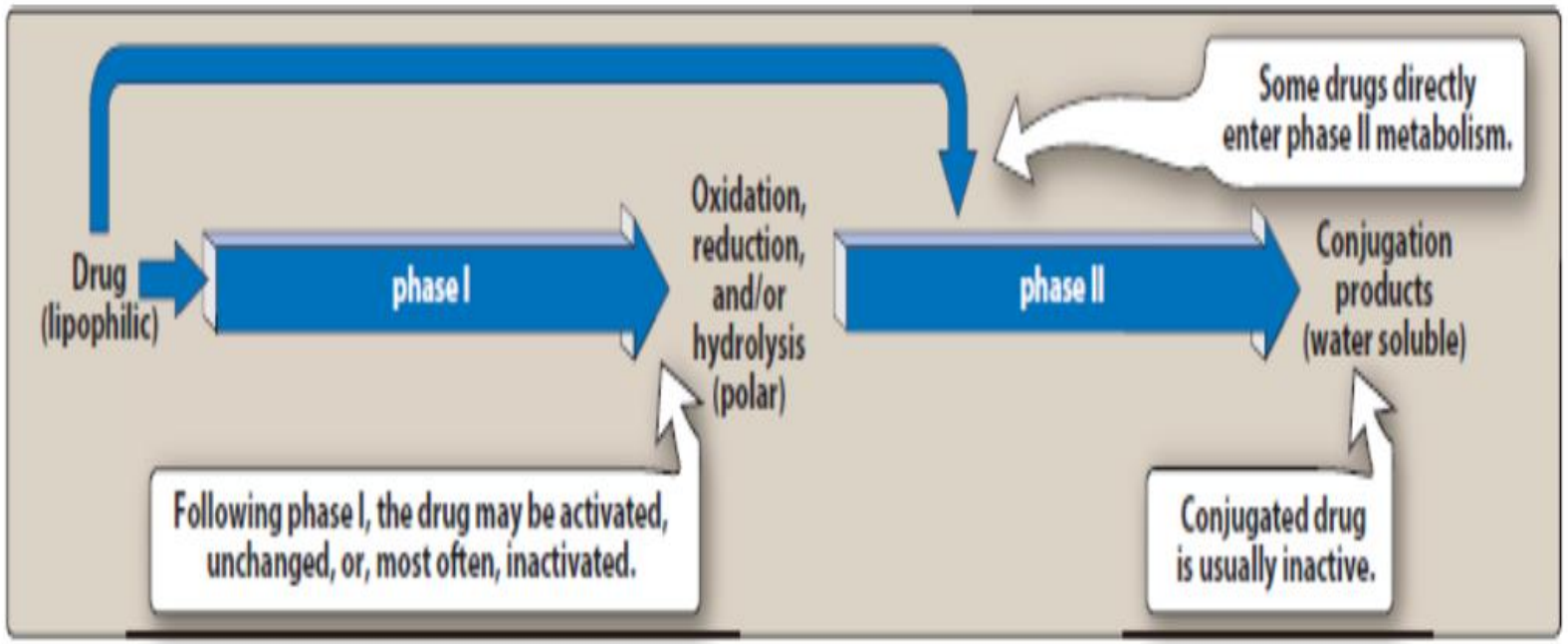


Figure: The biotransformation of drugs

Drug clearance through kidney:

Drugs must be sufficiently polar to be eliminated from the body. Removal of drugs from the body occurs via a number of routes, the most important being elimination through the kidney into the urine. Patients with renal dysfunction may be unable to excrete drugs and are at risk for drug accumulation and adverse effects.

Elimination of drugs via the kidneys into urine involves the processes of glomerular filtration, active tubular secretion, and passive tubular reabsorption.

1. Glomerular filtration:

Drugs enter the kidney through renal arteries, which divide to form a glomerular capillary plexus. Free drug (not bound to albumin) flows through the capillary slits into the Bowman space as part of the glomerular filtrate. The glomerular filtration rate (GFR) is normally about 125 mL/min but may diminish significantly in renal disease. Lipid solubility and pH do not influence the passage of drugs into the glomerular filtrate. However, variations in GFR and protein binding of drugs do affect this process.

2. Proximal tubular secretion: Drugs that were not transferred into the glomerular filtrate leave the glomeruli through efferent arterioles, which divide to form a capillary plexus surrounding the nephric lumen in the proximal tubule. Secretion primarily occurs in the proximal tubules by two energy-requiring active transport systems: one for anions (for example, deprotonated forms of weak acids) and one for cations (for example, protonated forms of weak bases). Each of these transport systems shows low specificity and can transport many compounds. Thus, competition between drugs for these carriers can occur within each transport system.

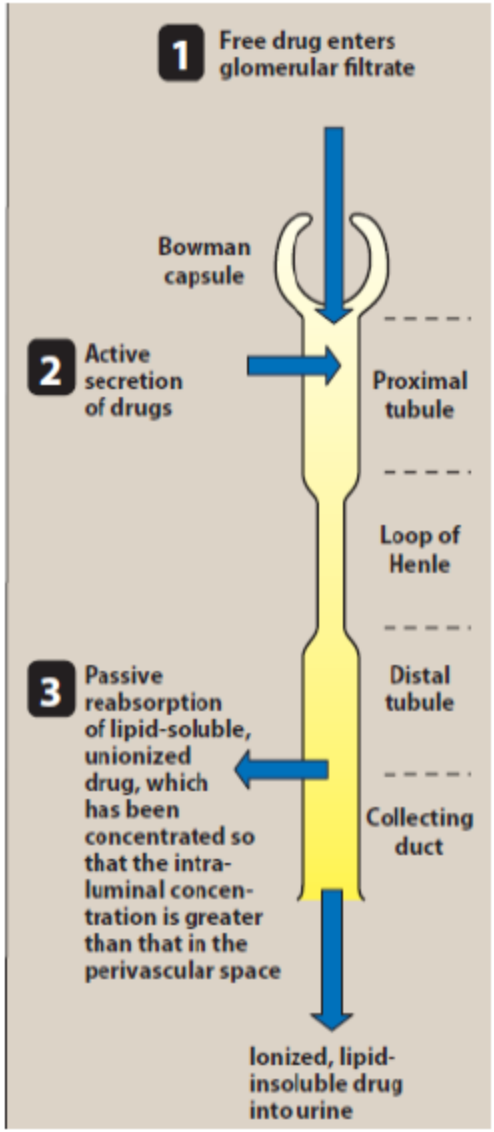


Figure: Drug elimination by the kidney

3. Distal tubular reabsorption: As a drug moves toward the distal convoluted tubule, its concentration increases and exceeds that of the perivascular space. The drug, if uncharged, may diffuse out of the nephric lumen, back into the systemic circulation. Manipulating the urine pH to increase the fraction of ionized drug in the lumen may be done to minimize the amount of back diffusion and increase the clearance of an undesirable drug. As a general rule, weak acids can be eliminated by alkalinization of the urine, whereas elimination of weak bases may be increased by acidification of the urine. This process is called "ion trapping." For example, a patient presenting with *phenobarbital* (weak acid) overdose can be given *bicarbonate,* which alkalinizes the urine and keeps the drug ionized, thereby decreasing its reabsorption.

Excretion by other routes:

Drug excretion may also occur via the intestines, bile, lungs, and breast milk, among others. Drugs that are not absorbed after oral administration or drugs that are secreted directly into the intestines or into bile are excreted in the feces. The lungs are primarily involved in the elimination of anesthetic gases (for example, desflurane). Elimination of drugs in breast milk may expose the breast-feeding infant to medications

and/ or metabolites being taken by the mother and is a potential source of undesirable side effects to the infant. Excretion of most drugs into sweat, saliva, tears, hair, and skin occurs only to a small extent. Total body clearance and drug half-life are important measures of drug clearance that are used to optimize drug therapy and minimize toxicity.

A. Total body clearance

The total body (systemic) clearance, Cl_{total}, is the sum of all clearances from the drug-metabolizing and drug-eliminating organs. The kidney is often the major organ of excretion. The liver also contributes to drug clearance through metabolism and/or excretion into the bile.

Total clearance is calculated using the following equation:

$$CL_{total} = CL_{hepatic} + CL_{renal} + CL_{pulmonary} + CLother$$

where $CL_{hepatic} + CL_{renal}$ are typically the most important.

B. Clinical situations resulting in changes in drug half-life

When a patient has an abnormality that alters the half-life of a drug, adjustment in dosage is required. Patients who may have an increase in drug half-life include those with 1) diminished renal or hepatic blood flow, for example, in cardiogenic shock, heart failure, or hemorrhage; 2) decreased ability to extract drug from plasma, for example, in renal disease; and 3) decreased metabolism, for example, when a concomitant drug inhibits metabolism or in hepatic insufficiency, as with cirrhosis. These patients may require a decrease in dosage or less frequent dosing intervals. In contrast, the half-life of a drug may be decreased by increased hepatic blood flow, decreased protein binding, or increased metabolism. This may necessitate higher doses or more frequent dosing intervals.

أسئلة وزارية

1. **The drugs can be administered by different routes of administration Which of the following routes of administration produce lower bioavailability?**

   A.Oral

   B.Sublingual

   C.Rectal

   D.Intramuscular

   E.Intravenous

2.Drug can penetrate the cell membrane by different mechanisms. Which of the following in not suitable for hydrophilic substance?

A.Simple diffusion

B.Active transport

C.Endocytosis

D.Exocytosis

E.All the above

أسئلة وزارية

3. **Drug distribution is the process by which a drug reversibly leaves the bloodstream and enters the extracellular fluid and tissues.**

   The following can decrease the volume of distribution for drug

   A. Lipophilicity
   B. Plasma Protein binding
   C. Low molecular weight
   D. Tissue protein binding
   E. All the above

أسئلة الفصل

1. An 18-year-old female patient is brought to the emergency department due to drug overdose. Which of the following routes of administration is the most desirable for administering the antidote for the drug overdose?

o Oral
o Subcutaneous
o Intramuscular
o Transdermal
o Intravenous

2. Drug A is a weakly basic drug with a pKa of 7.8. If administered orally, at which of the following sites of absorption will the drug be able to readily pass through the membrane?

o Duodenum (pH approximately 6.1)
o Stomach (pH of 2.5)
o Jejunum (pH approximately 8.0)
o Mouth (pH approximately 7.0)
o Ileum (pH approximately 7.0)

3. KR2250 is an investigational cholesterol-lowering agent. KR2250 has a high molecular weight and is extensively bound to albumin. KR2250 will have a(n) _____apparent volume of distribution (Vd).

o Low o Extremely hig o High o Normal

4. A 40-year-old male patient (70 kg) was recently diagnosed with infection involving

methicillin-resistant S. aureus. He received 2000 mg of vancomycin as an IV loading

dose. The peak plasma concentration of vancomycin was 28.5 mg/L. The apparent

volume of distribution is:

- 7 L/kg
- 10 L/kg
- 1 L/kg
- 14 L/kg
- 70 L/kg

5. A 55-year-old woman is brought to the emergency department because of seizures. She

has a history of renal disease and currently undergoes dialysis. She receives an

intravenous infusion of antiseizure Drug X. Which of the following is likely to be

observed with use of Drug X in this patient?

	Half-life	Dosage
A.	↑	↑
B.	↓	↓
C.	↑	↔
D.	↑	↓
E.	↔	↔

- o B
- o D
- o A
- o C
- o E

6. A 68-year-old woman is brought to the emergency department for treatment of a myocardial infarction. She is currently taking clopidogrel (antiplatelet agent) and aspirin daily, as well as omeprazole (potent CYP inhibitor) for heartburn. Which of the following is the most likely contributor to her myocardial infarction today?

o Hypersensitivity reaction due to clopidogrel
o Reduced antiplatelet activity of clopidogrel due to aspirin
o Reduced antiplatelet activity of clopidogrel due to omeprazole
o Increased antiplatelet activity of clopidogrel due to omeprazole
o Increased antiplatelet activity of clopidogrel due to aspirin

7. Which of the following reactions represents Phase II of drug metabolism?

o Oxidation o Sulfation o Reduction o Hydrolysis o Amidation

8. A pharmacokinetic study of a new antihypertensive drug is being conducted in healthy human volunteers. The half-life of the drug after administration by continuous intravenous infusion is 12 hours. Which of the following best approximates the time for the drug to reach steady state?

o 72 hours
o 120 hours
o 48 hours
o 24 hours
o 240 hours

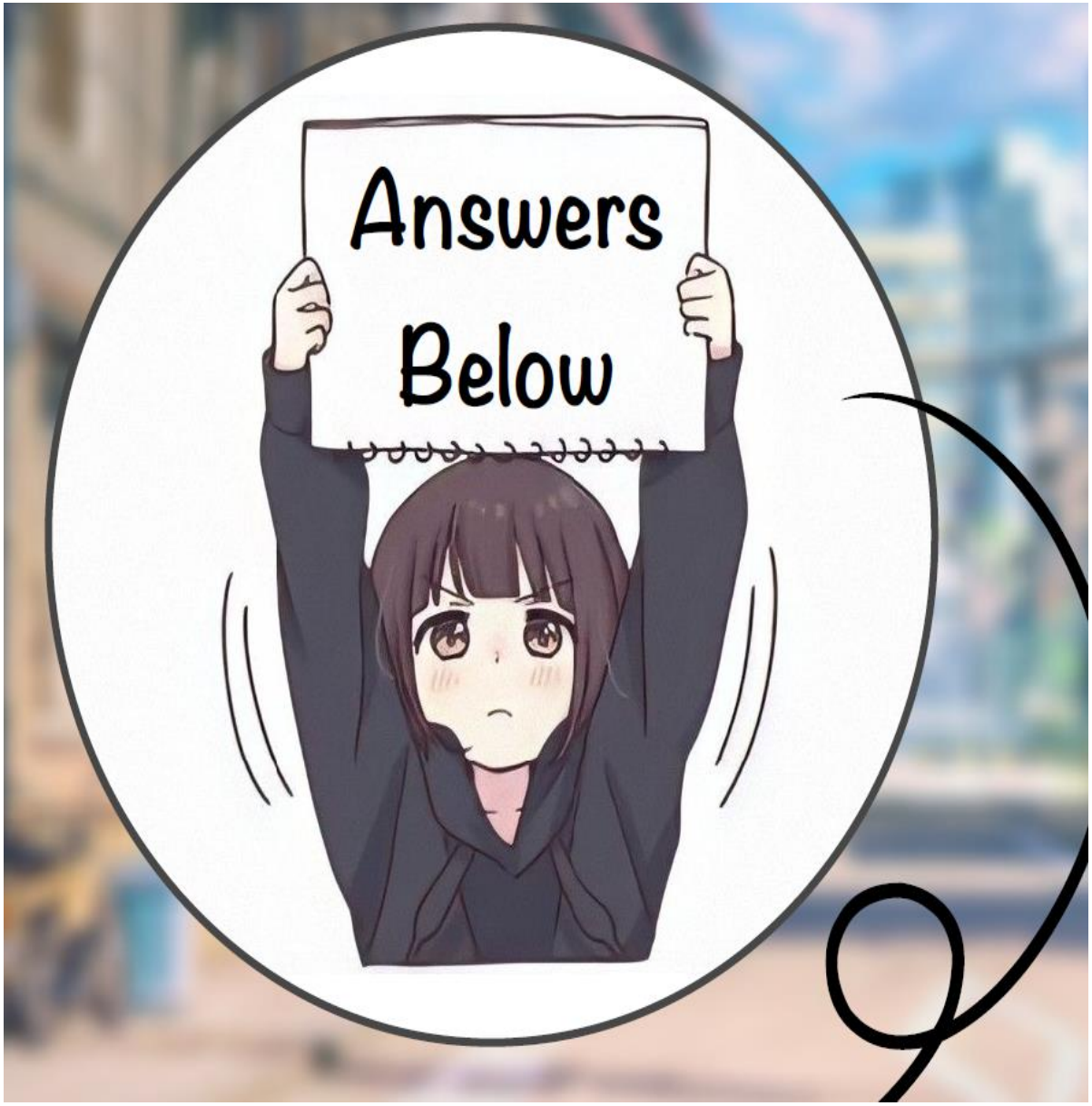
9. A 64-year-old female patient (60 kg) is treated with experimental Drug A for type 2 diabetes. Drug A is available as tablets with an oral bioavailability of 90%. If the Vd is 2 L/kg and the desired steady-state plasma concentration is 3.0 mg/L, which of the following is the most appropriate oral loading dose of Drug A?

o 6 mg
o 108 mg
o 360 mg
o 6.66 mg
o 400 mg

10. A 74-year-old man was admitted to the hospital for treatment of heart failure. He received 160 mcg of digoxin intravenously, and the plasma digoxin level was 0.4 ng/mL.

If the desired plasma concentration of digoxin for optimal therapeutic activity in heart failure is 1.2 ng/mL, and the patient has an estimated Vd of 400 L, calculate the additional dose of digoxin needed for this patient to achieve the desired plasma concentration.

o 480 mcg
o 128 mcg
o 160 mcg
o 320 mcg
o 640 mcg


Answers
Below

1.
Correct Response: Intravenous
Explanation: The intravenous route of administration is the most desirable because it results in achievement of therapeutic plasma levels of the antidote rapidly.
2.
Correct Response: Jejunum (pH approximately 8.0)
Explanation: Because Drug A is a weakly basic drug (pKa = 7.8), it will be predominantly in the nonionized form in the jejunum (pH of 8.0). For weak bases, the nonionized form will permeate through the cell membrane readily.
3.
Correct Response:Low
Explanation: Because of its high molecular weight and high protein binding, KR2250 will be effectively trapped within the plasma (vascular) compartment and will have a low apparent volume of distribution.
4.
Correct Response:1 L/Kg
Explanation:Vd = dose/C = 2000 mg/28.5 mg/L = 70.1 L. Because the patient is 70 kg, the apparent volume of distribution in L/kg will be approximately 1 L/kg (70.1 L/70 kg).
5.
Correct Response:D
Explanation: Because the patient has a renal disorder, she may not be able to excrete the drug effectively. Therefore, the half-life of Drug X will be prolonged. As the half-life is prolonged, the dosage must be reduced so the patient will not have serious toxic effects of Drug X.

6.Correct Response: Reduced antiplatelet activity of clopidogrel due to omeprazole
Explanation: Clopidogrel is a prodrug and requires CYP2C19 activity for conversion to an active metabolite. Because omeprazole is a potent CYP inhibitor, clopidogrel is not converted to the active metabolite, and therefore the antiplatelet activity is reduced, potentially contributing to myocardial infarction.

7.Correct Response: Sulfation
Explanation: Phase II metabolic reactions involve conjugation reactions to make phase I metabolites more polar. Sulfation and glucuronidation are the most common phase II conjugation reactions.

8.Correct Response:48 hours
Explanation: A drug will reach steady state in about 4 to 5 half-lives. Therefore, for this drug with a half-life of 12 hours, the approximate time to reach steady state will be 48 hours.
9.Correct Response:400 mg
Explanation: For oral dosing, loading dose = [(V d) × (desired steady-state plasma concentration)/F]. The Vd in this case is corrected to the patient's weight is 120 L. The F value is 0.9 (because bioavailability is 90%, that is, 90/100 = 0.9). Thus, loading dose = (120 L × 3.0 mg/L)/0.9 = 400 mg.

10.Correct Response:320 mcg
Explanation: The additional dosage of digoxin needed to achieve the desired plasma concentration can be calculated using the equation V d (C2-C1). C1 is the current plasma concentration (0.4 ng/mL) and C 2 is the desired plasma concentration (1.2 ng/mL). Therefore, the additional dosage of digoxin is [400 L × (1.2 – 0.4) ng/mL)] = 320 mcg..

Which of the following is the accurate method of eliminating a toxic dose of phenobarbital?

A)Alkalinization of urine

B)Administering bicarbonate to decrease urine PH

C)Acidification by NH4CL

D)Aministering ammonium chloride to increase urine PH

E) None of the above

A drug is given as 800 mg single dose, result in a peak plasma concentration of 40μg\ml the apparent volume of distribution is(assume a rapid distribution and negligible elimination prior to measuring the peak plasma level):

a) 0.2 L b) 1L c) 2L d) 5L e) 20L

Which of the following is related to P- glycoprotein expression?

a) Transporting drugs into cells b) Reducing drug resistance c) Reducing drug absorption d) metabolizing drugs e) All of the above

Which of the following conditions may be lead to an increased drug half life

a) Decreased plasma volume b) decreased renal blood flow c) decreased protein binding

d) Increased metabolism e) increased hepatic blood flow

If drug X has low molecular weight and hydrophilic , the drug will distribute to:

a) Extracellular fluid b) plasma compartment c) total body water d) plasma proteins e) intracellular compartment

Which route of administration is used to directly impact the central nervous system, by passing the bbb ?

A)oral b) intrathecal c) subcutaneous d) intranasal e) intravenous

which of the following is a phase I reaction involved in drug metabolism ?

A) Methylation b) Glucuronidation c) sulfation
d) oxidation e) acetylation