DEFINITIONS

Pharmacology: the science that studies the effect of chemical compounds (drugs, medicine) on the biological system (cells, organs..).

Pharmacy: the science or **practice** of the preparation and dispensing of medicinal drugs.

Pharmacist: : a health-care professional licensed to engage in pharmacy with duties including dispensing prescription drugs, monitoring drug interactions, administering vaccines, and counseling patients regarding the effects and proper usage of drugs and dietary supplements.

Toxicology: is the study of the adverse effects of chemicals (including drugs) on living systems and the means to prevent or ameliorate such effects. In addition to therapeutic agents, toxicologists examine many environmental agents and chemical compounds that are synthesized by humans or that originate in nature.

A pharmaceutical drug: also called a medication or medicine, is a chemical substance used to treat, cure, prevent, or diagnose a disease or to promote well-being. Traditionally drugs were obtained through extraction from medicinal plants, but more recently also by organic synthesis.

Pharmacokinetics: refers to what the body does to a drug.

DEFINITIONS (cont)

Pharmacodynamics: describes what the drug does to the body. MOA. the interaction between the drug and the target. structure-activity relationship of the drug.

Absorption: First, absorption from the site of administration permits entry of the drug (either directly or indirectly) into plasma. Its rate and efficiency depend on the route of administration. Complete 100% after IV administration.

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.

Bioavailability: Amount of the drug in the blood/amount of blood at the site of administration*100%. indicator for ABS.

Elimination half-life: is the length of time required for the concentration of a particular substance (typically a drug) to decrease to half of its starting dose in the body

DEFINITIONS (cont)

The duration of action of a drug: is the length of time that particular drug is effective. Duration of action is a function of several parameters including plasma half-life, the time to equilibrate between plasma and target compartments, and the off rate of the drug from its biological target.

Onset of action: is the duration of time it takes for a drug's effects to come to prominence upon administration. With oral administration, it typically ranges anywhere from 20 minutes to over an hour, depending on the drug in question.

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.

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.

ROUTES OF DRUG ADMINISTRATION (cont)

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.

Sponsored by **Readable.com**
Measure your website readability!
https://readable.com

ROUTES OF DRUG ADMINISTRATION (cont)

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.

ROUTES OF DRUG ADMINISTRATION (cont)

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 firstpass metabolism (see discussion of first-pass metabolism below). The buccal route (between the cheek and gum) is similar to the sublingual route.

ROUTES OF DRUG ADMINISTRATION (cont)

B. **Parenteral:** The parenteral route introduces drugs directly into the systemic circulation. 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.

ROUTES OF DRUG ADMINISTRATION (cont)

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.

Sponsored by **Readable.com**
Measure your website readability!
https://readable.com

ROUTES OF DRUG ADMINISTRATION (cont)

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 and depot medroxyprogesterone.

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.

ROUTES OF DRUG ADMINISTRATION (cont)

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.

ROUTES OF DRUG ADMINISTRATION (cont)

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.

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.

ROUTES OF DRUG ADMINISTRATION (cont)

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.

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

Sponsored by **Readable.com**
Measure your website readability!
https://readable.com

ABSORPTION OF DRUGS (cont)

1. **Passive diffusion:** The driving force for passive absorption of a drug is the concentration gradient across a membrane separating two body compartments. In other words, the drug moves from a region of high concentration to one of lower concentration. Passive diffusion does not involve a carrier, is not saturable, and shows a 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 their 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 and moving them from an area of high concentration to an area of low concentration. 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.

ABSORPTION OF DRUGS (cont)

3. **Active transport:** This mode of drug entry also involves specific carrier proteins that span the membrane. A few drugs that closely resemble the structure of naturally occurring metabolites are actively transported across cell membranes using specific carrier proteins. Energy-dependent active transport is driven by the hydrolysis of adenosine triphosphate. It is capable of moving drugs against a concentration gradient, from a region of low drug concentration to one of higher drug concentration. The process is saturable. Active transport systems are selective and may be competitively inhibited by other cotransported 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 drugfilled 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.

ABSORPTION OF DRUGS (cont)

B. **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 --> 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+ --> B + H+

ABSORPTION OF DRUGS (cont)

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. [Note: The pKa is a measure of the strength of the interaction of a compound with a proton. The lower the pKa of a drug, the more acidic it is. Conversely, the higher the pKa, the more basic is the drug.] Distribution equilibrium is achieved when the permeable form of a drug achieves an equal concentration in all body water spaces.

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. [Note: Shock severely reduces blood flow to cutaneous tissues, thereby minimizing absorption from SC administration.]

Sponsored by **Readable.com**
Measure your website readability!
https://readable.com

ABSORPTION OF DRUGS (cont)

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. [Note: The presence of food in the stomach both dilutes the drug and slows gastric emptying. Therefore, a drug taken with a meal is generally absorbed more slowly.]

5. **Expression of P-glycoprotein:** P-glycoprotein is a transmembrane transporter protein responsible for transporting various molecules, including drugs, across cell membranes (Figure 1.9). 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.

ABSORPTION OF DRUGS (cont)

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 70 mg is absorbed unchanged, the bioavailability is 0.7 or 70%. Determining bioavailability is important for calculating drug dosages for nonintravenous 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. The total AUC reflects the extent of absorption of the drug. Bioavailability of a drug given orally is the ratio of the AUC following oral administration to the AUC following IV administration

ABSORPTION OF DRUGS (cont)

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 the 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 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. 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 or transdermal 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.

ABSORPTION OF DRUGS (cont)

b. **Solubility of the drug:** Very hydrophilic drugs are poorly absorbed because of their inability to cross lipid-rich cell membranes. Paradoxically, drugs that are extremely lipophilic are also poorly absorbed, because they are totally 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.

c. **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.

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

Sponsored by **Readable.com**
Measure your website readability!
https://readable.com

ABSORPTION OF DRUGS (cont)

E. **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. [Note: Clinical effectiveness often depends on both the maximum serum drug concentration and the time required (after administration) to reach peak concentration. Therefore, two drugs that are bioequivalent may not be therapeutically equivalent.]

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.

DRUG DISTRIBUTION (cont)

A. Blood flow: The rate of blood flow to the tissue capillaries varies widely. For instance, blood flow to the “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.

DRUG DISTRIBUTION (cont)

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 be actively transported. For example, a specific transporter carries levodopa into the brain. By contrast, lipid--soluble drugs readily penetrate the CNS because they dissolve in the endothelial cell membrane. 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.

DRUG DISTRIBUTION (cont)

C. Binding of drugs to plasma proteins and tissues 1. Binding to plasma proteins: Reversible binding to plasma proteins sequesters drugs in a nondiffusible form and slows their transfer out of the vascular compartment. Albumin is the major drug-binding protein and may act as a drug reservoir (as the concentration of free drug decreases due to elimination, the bound drug dissociates from the protein). This maintains the free drug concentration

2. Binding to tissue proteins: Many drugs accumulate in tissues, leading to higher concentrations in tissues than in the extracellular fluid and blood. Drugs may accumulate as a result of binding to lipids, proteins, or nucleic acids. Drugs may also be actively transported 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.)

Sponsored by **Readable.com**
Measure your website readability!
https://readable.com

DRUG DISTRIBUTION (cont)

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. In contrast, hydrophilic drugs do not readily penetrate cell membranes and must pass through slit junctions.

E. Volume of distribution: The apparent volume of distribution, Vd, 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 (C0).

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.

DRUG DISTRIBUTION (cont)

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 Vd that approximates the plasma volume or about 4 L in a 70-kg individual. Heparin (see Chapter 22) 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 14 L in a 70-kg individual). Aminoglycoside antibiotics (see Chapter 39) show this type of distribution.

c. Total body water: If a drug has a low molecular weight and is lipophilic, it can move into the interstitium through the slit junctions and also 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 Vd.

DRUG DISTRIBUTION (cont)

2. Apparent volume of distribution: A drug rarely associates exclusively with only one of the water compartments of the body. Instead, the vast majority of drugs distribute into several compartments, often avidly binding cellular components, such as lipids (abundant in adipocytes and cell membranes), proteins (abundant in plasma and cells), and nucleic acids (abundant in cell nuclei). Therefore, the volume into which drugs distribute is called the apparent volume of distribution (Vd). Vd is a useful pharmacokinetic parameter for calculating the loading dose of a drug.

3. Determination of Vd: The fact that drug clearance is usually a first-order process allows calculation of Vd. 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 (Figure 1.14). 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 C0, which is the concentration of drug that would have been achieved if the distribution phase had occurred instantly.

DRUG DISTRIBUTION (cont)

4. Effect of Vd on drug half-life: Vd has an important influence on the half-life of a drug, because drug elimination depends on the amount of drug delivered to the liver or kidney (or other organs where metabolism occurs) per unit of time. Delivery of drug to the organs of elimination depends not only on blood flow but also on the fraction of the drug in the plasma. If a drug has a large Vd, most of the drug is in the extraplasmic space and is unavailable to the excretory organs. Therefore, any factor that increases Vd can increase the half-life and extend the duration of action of the drug. [Note: An exceptionally large Vd indicates considerable sequestration of the drug in some tissues or compartments.]

Sponsored by **Readable.com**
Measure your website readability!
https://readable.com