PHARMACOKINETICS

The quantitative study of drug transport in, through, and out of the body is known as pharmacokinetics.[1] Through ADME, four pharmacokinetic characteristics control the onset, magnitude, and duration of pharmacological effect. [2]

The membrane transport system is an approach for moving various substances through cell membranes. Cells have a variety of transport systems. Depending on whether molecules move through the lipid bilayer directly or via a membrane channel, whether or not the molecules are changed as they move across the membrane, and if the process needs energy, membrane transport systems may be categorized into two basic categories.

There are two main categories for membrane transport systems:
1. Passive transportation:
2. Active transportation:

1. Passive transportation:

Because the passive transport mechanism doesn't need cellular energy to carry molecules across the cell membrane, it is a passive process. In this transport mechanism, molecules are transferred until the concentration gradient is reduced from their higher concentration to the lower concentration. Passive transportation comprises:

(i) Passive diffusion or simple diffusion

ii) Osmosis

iii) facilitated diffusion

i. Passive diffusion or simple diffusion

Simple diffusion is the energy-free transportation or movement of molecules from a higher concentration to a lower concentration. Molecules just pass past the cell membrane's pore during this procedure. Transporter proteins are not necessary for simple diffusion. A concentration gradient is created when there are differences in the concentration of molecules inside and outside the cell membrane. When equilibrium is reached, the molecules migrate from a higher concentration to a lower concentration. The process of transport halts when the concentration of molecules on each side of the membrane reaches equilibrium. Sometimes, after entering the cell, molecules undergo metabolic changes that prevent the concentration of transported molecules from building up, maintaining the concentration gradient. Concentration gradient and cytoplasmic membrane permeability both affect how quickly molecules diffuse. The rate of

passive diffusion will increase with increasing concentration gradient and cell membrane permeability. For instance, gases or water can enter a bacterial cell by simple diffusion.

ii. Osmosis:

In response to a gradient in the concentration of the solute, a membrane-bound solvent (water) travels across it through the process of osmosis. More solutes are frequently present in bacterial cytoplasm than in the environment.

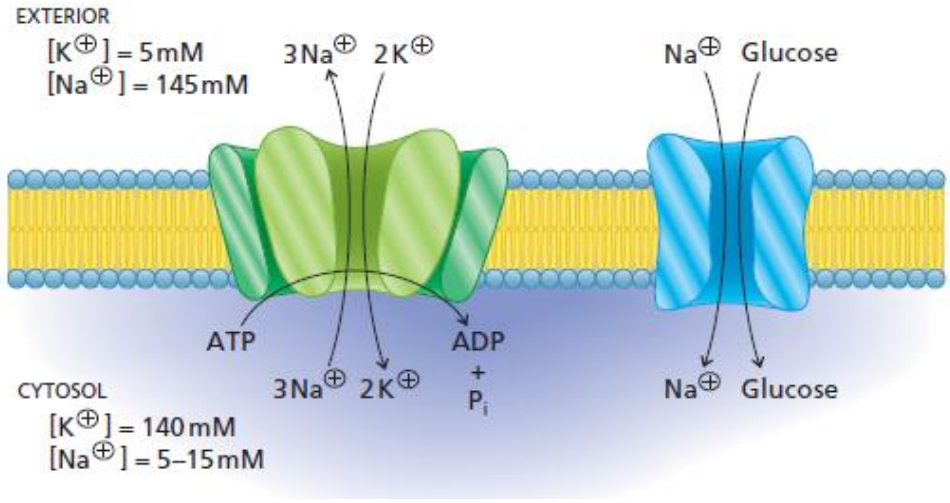
There are three different types of solutions, using the bacterial cytoplasmic concentration as a standard. A homogeneous water movement occurs both within and outside of cells in an isotonic solution. In a hypertonic solution, the cell contracts as a result of water evaporating from it. The process is referred to as plasmolysis. Water moves throughout the cell in a hypotonic solution, causing it to enlarge. The process is called plasmotysis.

iii. Facilitated diffusion:

Facilitated diffusion is similar to simple diffusion in that molecules move from areas of greater concentration to areas of lower concentration, but it differs from simple diffusion in that it calls on the presence of transporter proteins. Permease, Porter, or carrier protein are all names for the transporter protein. Even while certain transporter proteins may move more than one molecule, they are all specialized. The solute molecule initially interacts with the transporter protein, changing its three-dimensional (3D) form and enabling the solute to be transported across the membrane.

2. Active transportation:

The movement of molecules across a membrane's concentration gradient needs active transport, which calls for transporter proteins and a constant source of cellular energy. Transporting molecules with very low concentrations of presence in the medium requires active transport, which is crucial. In active transport, a permease or transporter protein moves the molecules across the membrane while ATP or an ion gradient provides the energy needed for the transport. The molecules that are carried via active transport include glucose, amino acids, organic acids, and inorganic ions (SO_4^-, PO_4^-, K^+, etc.). Examples include the lac operon, which helps E. coli transport lactose, and the NK pump.



Active transport system includes-

i) Primary active transport

ii) Secondary active transport

i. Primary active transport:

In primary active transport, hydrolysis of energy rich molecules such as ATP provide energy required for transport of molecules form lower concentration to higher concentration across membrane.

ii. Secondary active transport:

During secondary active transport, one kind of molecule goes from a higher concentration to a lower concentration, releasing energy in the process, while another type of molecule moves across the cell membrane from a lower concentration to a higher concentration utilizing the energy that was released.[6]

ABSORPTION

Absorption is the process by which a medicine travels from the site of administration to the bloodstream. The rate and extent of absorption are influenced by a number of factors, including the environment in which the medicine is absorbed, the chemical composition of the drug, the dosage form, and the method of administration (which impacts bioavailability). Other than intravenous dosing methods may cause incomplete absorption and reduced bioavailability. The medicine and patient-related aspects both play a role in determining the best course to take in a certain circumstance.

For instance, the medication's physical and chemical properties, its formulation (solid, liquid, or gas, or an aqueous solution, suspension, or oil), the dosage's precision, and how quickly the drug is absorbed and/or released; the duration of action for various medication delivery systems The targeted outcome, whether local, systemic, or aimed at achieving high concentration at a certain location.

Clinical emergency or routine treatment.Condition of the patient (unconscious or vomiting) [2]

Aqueous solubility Before being absorbed, drugs that are administered in solid form must dissolve in the aqueous biophase. The rate of dissolution determines the rate of absorption for medications with low water solubility (such as aspirin and griseofulvin). [1]

Concentration Drug administered in a concentrated solution is absorbed more quickly than from a diluted solution; passive diffusion is dependent on concentration gradient. [1]

Area of absorbing surface Faster absorption occurs when the surface area is greater. [1]

Vascularity of the absorbing surface Drugs are removed from the site of absorption by blood circulation, which also maintains the gradient of concentration throughout the absorbing surface. Similar to how wind speeds up clothing drying, increased blood flow speeds up medicine absorption. [1]

Route of administration Because each route has unique characteristics, this has an impact on medication absorption.[1]

The main routes of administration are:

Oral The lipoidal epithelial lining of the gastrointestinal system serves as an efficient barrier to medications taken orally. Alcohol and other nonionized lipid soluble medications are quickly absorbed from the stomach and intestine at rates inversely correlated with their lipid: water partition coefficient.[1]

Injection – subcutaneous – intramuscular – intravenous – intrathecal – intravitreal These approaches result in the medication being directly deposited close to the capillaries. Drugs that are lipid soluble easily traverse the capillary endothelium's whole surface. massive paracellular gaps in capillaries prevent even massive, lipid-insoluble molecules or ions from being absorbed. Through lymphatics, very big molecules are absorbed.

Application to other epithelial surfaces (e.g. skin, cornea, vagina and nasal mucosa) After topical administration, a drug's ability to dissolve in lipids is a major factor in systemic absorption. Only a small number of medications, nevertheless, significantly penetrate undamaged skin. [1]

Sublingual Despite the little surface area available, absorption via the mouth mucosa has unique relevance for several medications. The superior vena cava receives venous drainage from the mouth, shielding the medication from hepatic first-pass metabolism. For instance, nitroglycerin, which is nonionic and has a high lipid solubility, works well when held sublingually. The medication is absorbed very quickly as a result.[5]

Rectal When vomiting is prevalent or oral intake is impossible due to the patient's unconsciousness, the rectal route is frequently helpful. This is especially true for small children. Since the liver is bypassed by around 50% of the medication that is absorbed through the rectum, there is less chance of hepatic first-pass metabolism than there is for an oral dosage. However, many medications can irritate the rectal mucosa, and rectal absorption is frequently inconsistent and partial. [5]

Inhalation Gaseous and volatile medications can be breathed and absorbed via the pulmonary epithelium and mucous membranes of the respiratory tract as long as they don't irritate the respiratory tract. This method provides quick circulatory access because to the lung's enormous surface area.[5]

BIOAVAILABILITY

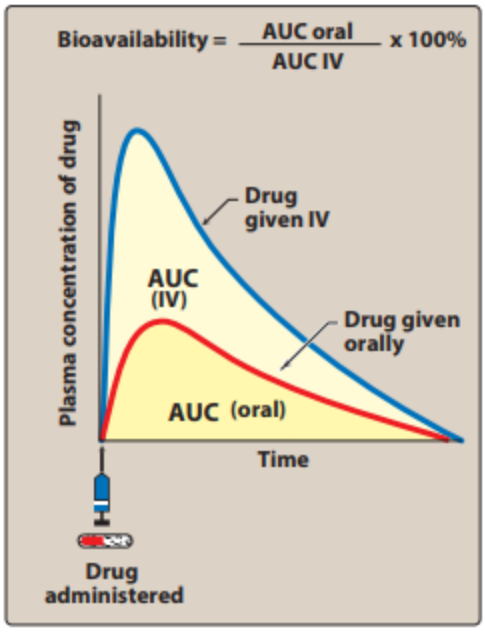
The term "bioavailability" describes the proportion of an oral dose (F) that, following absorption and local metabolic breakdown, enters the systemic circulation as an intact drug.[4]

It is a measurement of the percentage (F) of a drug's given dosage that enters the systemic circulation unaltered. 100% of the medication administered intravenously is bioavailable. [1]

Calculating medication doses for nonintravenous methods of delivery requires knowledge about bioavailability. [2]

Determination of bioavailability: By comparing the plasma levels of a medication following a certain method of administration (for instance, oral administration) with the levels attained by IV administration, bioavailability is identified. 100% of the medication reaches the bloodstream quickly after IV injection. When a medication is taken orally, only a portion of the supplied dosage enters the bloodstream. The area under the curve (AUC) may be calculated by graphing the drug's plasma concentrations vs time.

A schematic depiction of determination of bioavailability is provided in the figure below. [2]



Bioequivalence

When the rate and extent of the active drug's bioavailability from two drug preparations under appropriate test settings are not significantly different from one another, they are said to be bioequivalent. [1]

DISTRIBUTION

The process by which a medication reversibly exits the circulation and reaches the extracellular fluid and tissues is known as drug distribution. For medications given intravenously (IV), absorption is not a concern; instead, the first phase that occurs right after administration is the distribution phase, during which the medication quickly exits the circulation and enters the tissues.[2] The extent and pattern of distribution of a drug depends on its:

- Solubility of lipids

•ionization (as a function of its pKa) at physiological pH

• the degree of binding to tissue and plasma proteins

• tissue-specific transporters are present

• geographic variations in blood flow.

Physiological barriers to Drug Distribution

Blood Brain Barrier Paul Ehrlich developed the idea of the blood-brain barrier to explain his discovery that intravenously administered dye stained most tissues but not the brain. A continuous layer of endothelial cells connected by tight junctions and encircled by pericytes makes up the barrier. Many medications are therefore unable to reach the brain because their lipid solubility is inadequate to allow them to cross the blood-brain barrier. However, inflammation has the potential to compromise the blood-brain barrier's integrity, enabling substances that are ordinarily impermeable to enter the brain.[4]

Blood – CSF - Brain Barrier Brain capillary endothelial cells lack significant paracellular gaps and have tight connections. Furthermore, the capillaries are covered by an investment of brain tissue. They make up the blood-brain barrier, or BBB, as a whole. The choroid plexus contains a comparable blood-CSF barrier, with capillaries bordered by choroidal epithelium with tight connections. Both of these lipoidal barriers prevent the entrance of nonlipidsoluble medications like streptomycin and neostigmine. [1]

Placental Barrier Because medications may result in malformations in the growing baby, the transfer of pharmaceuticals through the placenta is crucial. They may also have negative effects on the newborn if given right before birth, which is frequently the case when tocolytics are used to treat premature labor. Important general factors that affect how well drugs cross the placenta include the solubility of the drug in lipids, the amount of plasma binding, and the degree of ionization of weak acids and bases. Since the fetal plasma has a pH between 7.0 and 7.2 compared to the mother's 7.4, basic medicines are ion trapped. P-gp and other export transporters are found in the placenta, just like in the brain, and they serve to reduce the exposure of the fetus to potentially harmful substances.[5]

VOLUME OF DISTRIBUTION

The fluid volume needed to hold the complete dose of the medication in the body at the same concentration as detected in the plasma is known as the apparent volume of distribution, or Vd. By dividing the plasma concentration at time zero (C0) by the dosage that eventually enters the systemic circulation, it is computed.

V = dose administered / plasma concentration

Vd has no physiological or physical foundation, although it might be helpful to compare medication distribution to the body's water compartment contents. [2]

Plasma-Protein Binding The majority of medications have a physicochemical affinity for plasma proteins and bind to them in a reversible manner. Basic medications often attach to 1 acid

glycoprotein, whereas acidic drugs typically bind to plasma albumin. The clinically significant implications of plasma protein binding are: [1]

(i)Because protein-bound medicines cannot pass membranes (other than through significant paracellular gaps), they are primarily limited to the vascular compartment.

(ii) The bound fraction isn't usable for doing anything.

(iii) Because the bound fraction is not immediately available for metabolism or excretion until it is actively retrieved by the liver or by renal tubules, drugs with a high degree of protein binding often have a long half-life. Drug clearance is accelerated in this circumstance by plasma protein binding, for example, by the excretion of penicillin (30 min for elimination) and by the metabolism of lidocaine. Haemodialysis cannot remove highly protein-bound medicines, hence additional methods are required to treat poisoning.

(iv) The medication's plasma concentrations are often stated in terms of both bound and free drug.

(v) There are several places on the albumin molecule where a medication might bind. [1]

METABOLISM

The term "biotransformation" also applies to metabolism. The term "biotransformation" describes how a medicine changes chemically as it enters the body. Making polar (lipid-insoluble) chemicals essential in order to keep nonpolar (lipid-soluble) compounds from being reabsorbed into the renal tubules and permitting excretion. For instance, relatively little biotransformation occurs when streptomycin, neostigmine, pancuronium, and other hydrophilic drugs are used, and they are often eliminated intact. [1]

Drug metabolism mostly occurs in the liver, although it can also occur in the kidney, stomach, lungs, and plasma. [1]

Although a molecule with pharmacological action may occasionally be formed, the final effect of drug metabolism is deactivation. The four ways a drug's metabolism might change its effects are as follows: [4]

1.The most typical sort of metabolic transition is from an active medication to an inactive metabolite.

Phenobarbitone ------ Hydroxyphenobarbitone
Phenytoin-------- p-Hydroxyphenytoin

2. Drug to active metabolite conversion:

Codeine--------Morphine
Diazepam------- Oxazepam

3. Drug from inactive to active metabolite:

L-Dopa--------- Dopamine
Prednisone------- Prednisolone

4. Active drug to highly toxic metabolite:

Paracetamol --------N-acetyl-p-benzoquinoneimine (NAPQI) [4]

Pathways of Drug Metabolism:

The reactions to drug metabolism occur in two phases. Phase II reactions are synthetic, as opposed to phase I reactions, which are not. [4]

Reactions in phase I (Table 1)

Oxidation: is the process of adding oxygen or removing hydrogen. The most significant and typical metabolic response is this one.

Reduction: Subtracting oxygen or introducing hydrogen.

Hydrolysis: Compound breakdown caused by water addition. Esters and amides are prone to this.

The metabolite may or may not be active at the conclusion of phase I. [4]

Oxidation	Phenytoin, phenobarbitone, propranolol, pentobarbitone
Reduction	Chloramphenicol, methadone
Hydrolysis	Esters - procaine, succinylcholine Amides - lignocaine, procainamide

Table 1. Phase I reaction

Phase II reactions (Table 2)

Reactions that include conjugation make up Phase II. If the phase I metabolite is polar, the kidneys will remove it. Numerous metabolites undergo conjugation with an endogenous substrate, such as glucuronic acid, sulphuric acid, acetic acid, or an amino acid, which results in their resorption. Usually inactive, polar, and water soluble, these conjugates. [4]

Glucuronide conjugation	Morphine, Paracetamol
Acetylation	Isoniazid, dapsone
Glycine conjugation	Salicylic acid, nicotinic acid
Sulphate conjugation	Paracetamol, sex steroids
Glutathione conjugation	Paracetamol
Methylation	Adrenaline, dopamine

Table 2. Phase II reactions

Phase I and phase II reactions to drugs don't always occur in that order. Phase II reaction occurs before phase I reaction in the case of isoniazid (INH).

1. Microsomal enzyme systems and non-microsomal enzyme systems are the two broad categories into which they may be divided.

2. Cellular enzymes: These enzymes are found mostly in the cells' endoplasmic reticulum. They catalyze the majority of phase I reactions as well as the phase II glucuronide conjugating reaction. Cytochrome P450, glucuronyl transferase, and other enzymes are among them. Microsomal enzymes can be induced.

3. Non-microsomal enzymes: They are present in the cytoplasm, liver cell mitochondria, and plasma. Except for glucuronide conjugation, these enzymes catalyze all phase II processes. Non-microsomal enzymes perform certain oxidative processes, as well as the majority of reduction and hydrolytic reactions. These enzymes are generally polymorphic and cannot be induced.

Enzyme induction Recurring doses of several medications increase the synthesis of microsomal enzymes. Enzyme induction is the term for this. Rifampicin, phenytoin, barbiturates, carbamazepine, griseofulvin, and other drugs fall under the category of "enzyme inducers." [4]

Clinical importance of enzyme induction

1.In some cases, such as with rifampicin X oral contraceptives, enzyme induction may accelerate drug metabolism, shortening the time and intensity of pharmaceutical activity. Oral contraceptives' drug-metabolizing enzyme is stimulated by rifampicin, which causes their metabolism to rise and their effectiveness to be compromised.
2. Drug tolerance may develop as a result of autoinduction, such as with carbamazepine.
3. Medication toxicity can be caused by enzyme induction; for instance, a greater incidence of hepatotoxicity with paracetamol in alcoholics is due to hazardous metabolite overproduction.
4. Long-term use of phenytoin may cause osteomalacia due to an increased metabolism of vitamin D3.
5. Porphyria can be precipitated by enzyme inducers due to porphobilinogen overproduction.
6. Vegetables such as cabbage, spinach, and others can stimulate microsomal enzymes and enhance medication excretion.
7. The activation of the glucuronyl transferase enzyme by phenobarbitone in newborns with jaundice causes the conjugation of bilirubin and remission of the jaundice, demonstrating the benefit of enzyme induction. [4]

Enzyme inhibition Enzyme inhibitors are medications that block the action of drug metabolizing enzymes. Enzyme inhibition is a faster process than enzyme induction, as shown by chloramphenicol, ciprofloxacin, erythromycin, etc.

The clinical significance of enzyme inhibition

Warfarin increases the risk of bleeding when used with erythromycin or chloramphenicol, for example. These drugs prevent warfarin from being metabolized by its drug-metabolizing enzyme, which raises warfarin plasma concentrations and intensifies its anticoagulant activity (bleeding).

Factors Affecting Drug Metabolism

1. Age: Neonates and the elderly metabolize some medications less efficiently than adults. Reduced hepatic microsomal enzyme activity is what causes the impairment in both cases. Neonatal toxicity-grey baby syndrome results from neonates conjugating chloramphenicol more slowly. Due to a compromised hepatic metabolism, the elderly are more likely to have propranolol and lignocaine poisoning.

2. Diet: A lack of protein inhibits drug metabolism. Protein-rich foods boost theophylline and caffeine metabolism, but carbohydrate-rich foods slow it down.

3. Diseases : Some medications' hepatic metabolism may be affected by chronic liver illnesses, such as diazepam's enhanced duration of action in individuals with cirrhosis.

4. Genetic variables (pharmacogenetics): These factors have an impact on drug metabolism as well. The study of genetic diversity in pharmaceutical response is known as pharmacogenetics. Drug metabolism rates may vary in genetically atypical individuals. For example;

(a) Isoniazid slow and fast acetylators: Slow acetylators have an increased risk of peripheral neuritis while using isoniazid. Fast acetylators need a higher dosage of the medicine to provide a therapeutic effect.

(b) Neuromuscular blocker and depolarizer succinylcholine is the cause of succinylcholine apnoea. It is metabolized by plasma pseudocholinesterase. Succinylcholine has an action time of 3-6 minutes. However, some people have atypical pseudocholinesterase, which causes the medication to be metabolized very slowly. This causes deadly prolonged apnea owing to paralysis of breathing muscles. This is referred to as succinylcholine apnoea.

(c) Hemolytic anemia with glucose-6-phosphate dehydrogenase (G6PD) deficiency: RBC integrity depends on G6PD activity. When exposed to specific medicines such as sulphonamides, primaquine, salicylates, dapsone, and others, a person with G6PD deficiency may experience haemolysis. [4]

FIRST PASS (PRESYSTEMIC) METABOLISM

When a medication moves from the site of absorption to the systemic circulation, its metabolism is referred to as transit metabolism. In the liver and intestinal wall, where they are initially

absorbed through the portal vein, all drugs taken orally are vulnerable to drug metabolizing enzymes.Presystemic metabolism in the gastrointestinal tract and liver can be stopped by administering the medicine parenterally, sublingually, or topically. However, for medications given transdermally and reaching venous circulation via either route, little presystemic metabolism can occur in the lungs and skin, respectively. The degree of first pass metabolism varies depending on the medicine, and it plays a significant role in determining oral bioavailability.[1]

EXCRETION

Drugs must have enough polarity to be excreted from the body. Drugs can be removed from the body in a number of ways, but kidney-to-urinary elimination is the most crucial. If a medicine is mostly excreted through the kidneys, patients with renal dysfunction may be unable to do so, putting them at risk for drug buildup and negative consequences. Additionally, drugs are expelled in saliva, bile, perspiration, lungs, breast milk, tears, and sexual secretions. [2]

1. Through the kidney, urinate. For the majority of medications, it is the most significant route of excretion.

2. Faeces The majority of the medication found in feces, aside from the unabsorbed portion, comes from bile. Organic acids (particularly drug glucuronides via OAT and MRP2), organic bases (by OCT), other lipophilic medicines (by P-gp), and steroids are all actively transported into bile by the liver through several non-specific active transport pathways. In the bile, relatively bigger molecules (MW > 300) are preferentially removed. The majority of the free drug in the gut, including that produced by enteric bacteria when they deconjugate glucuronides, is reabsorbed (enterohepatic cycling), and its final excretion takes place in urine. Only the remainder is eliminated by feces.

3. Breath of air Regardless of their solubility in lipids, gases and volatile liquids (such as alcohol and general anesthetics) are expelled by the lungs. The gas or vapour's alveolar transport is dependent on its blood partial pressure. The function of the lungs is to capture and expel any particles that enter the bloodstream.

5. Sweat and saliva These little affect the excretion of drugs. These secretions contain significant amounts of rifampin, lithium, potassium iodide, and heavy metals. Similar to an oral pill, the bulk of the medication in saliva is swallowed along with it.

6. Milk The medicine is accidentally given to the nursing infant even if the mother does not care whether the drug is excreted in milk. Most medicines passively diffuse into breast milk. Thus, medicines that are more lipid soluble and less protein bound pass more well. Basic medicines are somewhat more concentrated in milk, which has a lower pH (7.0) than plasma. The majority of

medications can be administered to nursing moms without harming the baby, and the overall quantity of drug that gets to the newborn through breastfeeding is often low. [1]

Renal elimination of a drug Before a medicine is excreted, it goes through the kidney's glomerular filtration, active tubular secretion, and passive tubular reabsorption processes.

1. Glomerular filtration: Drugs are supplied to the kidney by renal arteries, which divide to form a glomerular capillary plexus. Unbound medicines that are not bound to albumin flow through the capillary slits and into the Bowman space as part of the glomerular filtrate. The glomerular filtration rate (GFR), which is normally in the range of 125 mL/min, may significantly decrease in cases of renal disease or be adversely affected in the elderly and those with diabetes. Drug entry into the glomerular filtrate is unaffected by lipid solubility or pH. However, this mechanism is affected by differences in GFR, renal blood flow, and drug protein binding. Acute renal failure can be brought on by a drop in blood volume, nephrotoxic medications, or certain disorders, all of which can affect how quickly a substance is delivered to the kidney for removal. Fluoroquinolones and gentamicin have high renal excretion; as a result, the dosages of these medications should be cut in half if the GFR is less than 30 ml/min.

2. Proximal tubular secretion: Medications that were not delivered into the glomerular filtrate exit the glomeruli by efferent arterioles, which divide to form a capillary plexus around the nephric lumen in the proximal tubule. The proximal tubules' primary mechanism for secretion is two energy-intensive active transport processes, one for anions (such as deprotonated forms of weak acids) and one for cations (such as protonated forms of weak bases). Each of these transporters is only moderately selective and capable of transporting a large range of substances.

3. Distal tubular reabsorption: A drug's concentration rises and surpasses the perivascular space as it travels toward the distal convoluted tubule. If the medication is not charged, it may diffuse back into the systemic circulation from the nephric lumen. To reduce the quantity of back diffusion and boost the clearance of an undesired medication, the pH of the urine can be adjusted to raise the proportion of ionized drug in the lumen. In general, weak acids may be removed by alkalinizing the urine, whereas weak bases can be eliminated more effectively by acidifying the urine. "Ion trapping" is the name of this procedure.[2]

KINETICS OF ELIMINATION

The basis for creating logical dose regimens and modifying them to suit individual needs is understanding of the kinetics of elimination of a medication. It is important to comprehend the three basic pharmacokinetic characteristics of bioavailability (F), volume of distribution (V), and clearance (CL). The first two have been taken into account.

Total body clearance

The amount of plasma that is cleared per unit of time depends on the drug's clearance. The amount lost is directly related to the drug's bloodstream concentration.
The sum of all clearances from the organs that metabolize and eliminate drugs is known as the whole body (systemic) clearance, or CLtotal. The kidney is frequently the main excretory organ. Through metabolism and/or excretion into the bile, the liver also aids in the removal of drugs from the body. The following equation is used to get the total clearance:

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

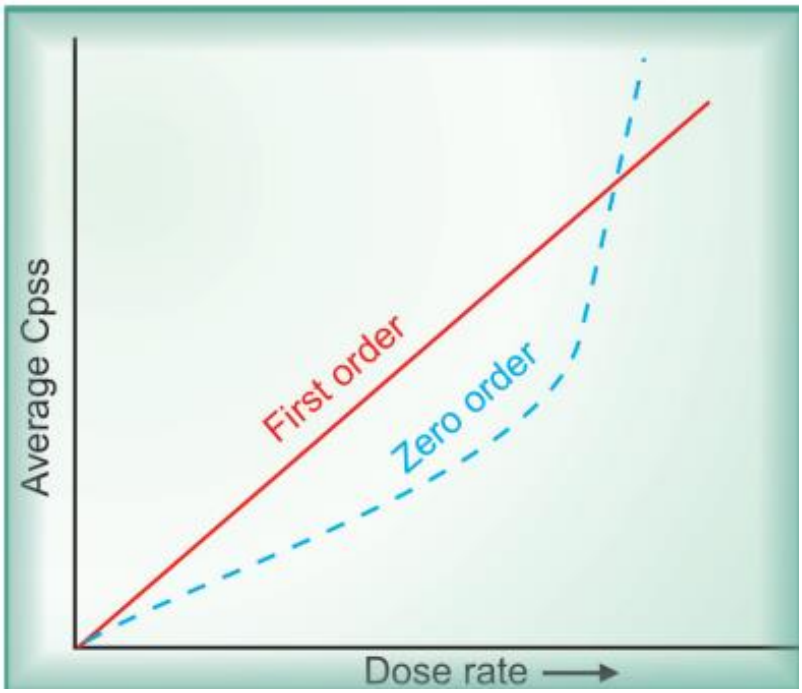
where CLhepatic + CLrenal are typically the most important. Care should be exercised while administering. [2]

First order kinetics

If the rate of elimination is directly proportional to the drug concentration, a constant amount of the drug that is already present in the body is eliminated in a given period of time. This holds true for the majority of pharmaceuticals as long as they don't overload the systems that remove them (transporters, enzymes, blood flow, etc.) above the therapeutic concentration limit.

Zero order kinetics

A fixed amount of the drug is removed in a unit of time, for example, ethyl alcohol, or the rate of elimination decreases with an increase in drug concentration. Additionally known as Michaelis-Menten elimination or capacity constrained elimination. Over the therapeutic range, the elimination of certain medicines approaches saturation; at greater dosages, the kinetics shift from first order to zero order. As a result, as is the case with phenytoin, tolbutamide, theophylline, and warfarin, plasma concentration rises disproportionately with an increase in dosage.



Relationship between dose rate and average steady-state plasma concentration of drugs eliminated by first order and Michaelis Menten (zero order) kinetics.

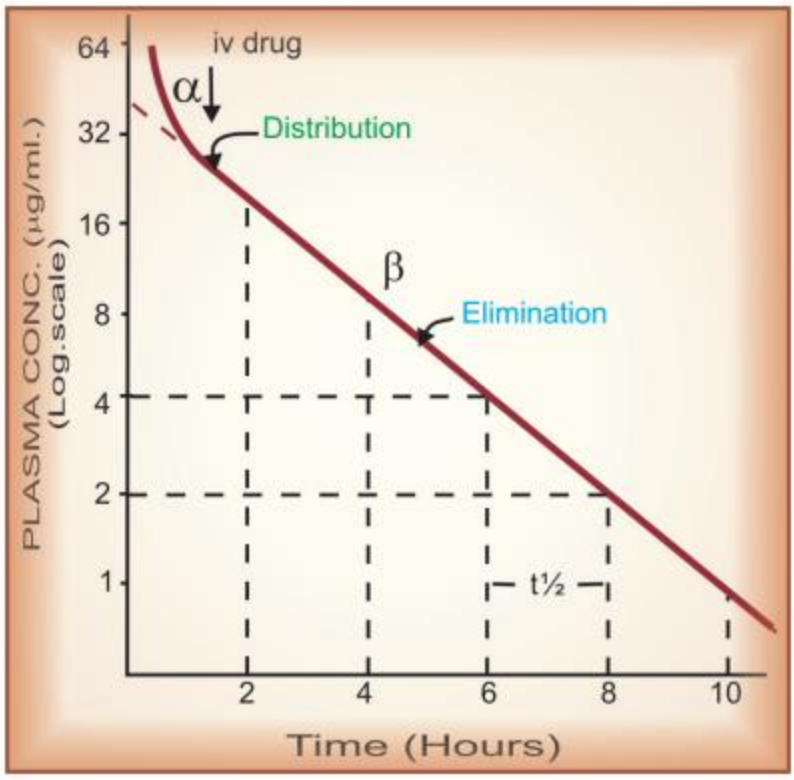
Plasma half-life

The time it takes for a drug's plasma concentration to decrease to half of what it was originally is known as the plasma half-life (t12). When an injectable drug with a rapid one compartment distribution and first order elimination is injected, a semilog plasma concentration-time plot, as seen in the image, is created. The plot has two slopes.

• initial rapidly declining (α) phase—due to distribution.

• later less declined (β) phase—due to elimination.

From the two slopes, at least two half-lives (distribution t1 and elimination t1) may be estimated. The drug's "half life" is the term used to refer to the elimination half-life calculated from the slope. [1]



Semilog plasma concentration-time plot of a drug eliminated by first order kinetics after intravenous injection

Significance of plasma t1/2:

• The determination of the dosage plan and dosing frequency is aided by plasma t1/2.

• For logical prescription or to comprehend the temporal course of adverse events, plasma t1/2 is helpful.

•The quantity of drug cleared in zero-order kinetics, where a constant amount of the drug is removed per unit time, is independent of the amount to be cleared. Examples of drugs with zero-order kinetics are ethanol and phenytoin. Toxicity occurs when these medications are administered repeatedly over brief periods of time. Therefore, receiving dialysis is the only approach to quicken the elimination process.[2]

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