**PHARMACOKINETICS**

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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 method for transporting different chemicals through cell membranes is known as the membrane transport system. Different transport mechanisms exist in cells. Membrane transport systems are divided into two main groups depending on whether molecules travel through the lipid bilayer directly or through a membrane channel, if the molecules are transformed as they pass through the membrane, and whether or not the process requires energy.**

Membrane transport system is categorized into two major groups:

1. **Passive transport:**
2. **Active transport:**
3. **Passive transport:**

It is a passive process because the passive transport mechanism does not use cellular energy to move molecules across the cell membrane. In this transport system, molecules are moved from their higher concentration to the lower concentration until the concentration gradient is lessened. Passive transport includes-

i) Simple diffusion or passive diffusion

ii) Osmosis

iii) Facilitated diffusion

**i. 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:**

Osmosis is the process by which a membrane-bound solvent (water) moves across it in response to a gradient in the solute's concentration. Bacterial cytoplasm often contains more solutes than its surroundings.

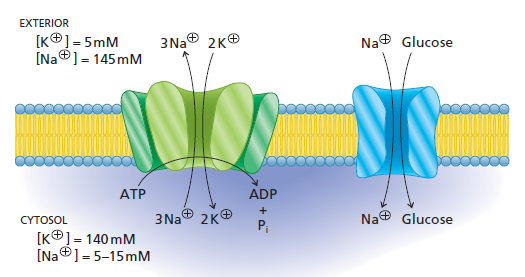
Using the bacterial cytoplasmic concentration as a benchmark, there are three different sorts of solutions. Water in an isotonic solution moves uniformly both inside and outside of cells. In a hypertonic solution, water leaves the cell, causing it to contract. Plasmolysis is the term for the action. In a hypotonic solution, water travels within the cell, causing it to swell. Plasmotysis is the process' name.

**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 transport:**

Active transport requires transporter protein and continuous supply of cellular energy for the transport of molecules across concentration gradient of the membrane. Active transport is very important to transport the molecules which are present in very low concentration in the medium. In active transport permease or transporter protein carries the molecules across the membrane and the energy required to transport is obtained by ATP or Ion gradient. The substances transported by active transport are glucose, aminoacids, organic acids and inorganic ions (SO4–, PO4–, K+ etc). Examples: Lac operon (transport of lactose in E. coli),  Na-K 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:**

One kind of molecule moves from a higher concentration to a lower concentration during secondary active transport, releasing energy in the process. Other molecules are moved across the cell membrane from a lower concentration to a higher concentration using the energy that was released. [6]

**ABSORPTION**

The movement of a medication from the place of administration to the bloodstream is known as absorption. The environment in which the medication is absorbed, the chemical makeup of the drug, the dose form, and the route of administration (which affects bioavailability) all have an impact on the pace and degree of absorption. 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**

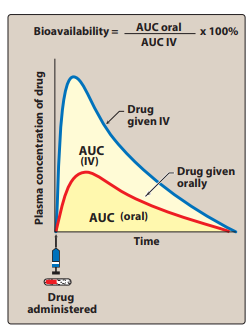
The word "bioavailability" refers to the percentage (F) of an oral dosage that, after being absorbed and subjected to local metabolic breakdown, enters the systemic circulation as an intact medication.[4]

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:

• lipid solubility

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

• extent of binding to plasma and tissue proteins

• presence of tissue-specific transporters

• differences in regional 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]

The end result of drug metabolism is inactivation, although occasionally a molecule with pharmacological activity may be produced. A drug's metabolism has the capacity to alter its effect in four different ways: [4]

**1.Active drug to inactive metabolite:** This is the most common type of metabolic transformation.

Phenobarbitone ------ Hydroxyphenobarbitone

Phenytoin-------- p-Hydroxyphenytoin

**2. Active drug to active metabolite:**

Codeine--------Morphine

Diazepam------- Oxazepam

**3. Inactive drug 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

Not all medications go through phase I and phase II responses in that sequence. In the case of isoniazid (INH), phase II reaction comes before phase I reaction .

They are roughly classified into two types: microsomal enzyme systems and non-microsomal enzyme systems.

1. **Microsomal 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.
2. **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** Certain medicines, when administered repeatedly, enhance the production of microsomal enzymes. This is referred to as enzyme induction. The medicine is known as an enzyme inducer, and examples include rifampicin, phenytoin, barbiturates, carbamazepine, griseofulvin, and others. [4]

**Clinical importance of enzyme induction**

1 Enzyme induction may increase drug metabolism, reducing the duration and intensity of medication activity and hence contributing to therapeutic failure, for example, rifampicin x oral contraceptives. Rifampicin stimulates the drug-metabolizing enzyme of oral contraceptives, resulting in increased metabolism and contraceptive failure.

2. Autoinduction, for example, carbamazepine, may result in the development of drug tolerance**.**

3. Enzyme induction can result in medication toxicity; for example, a higher incidence of hepatotoxicity with paracetamol in alcoholics is attributable to hazardous metabolite overproduction.

4. Prolonged phenytoin medication may result in osteomalacia due to increased vitamin D3 metabolism.

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. Enzyme induction can also be advantageous, for example, phenobarbitone in newborn jaundice-phenobarbitone activates the glucuronyl transferase enzyme, resulting in bilirubin conjugation and resolution of jaundice. [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 medications block the drug metabolizing enzyme of warfarin, resulting in higher warfarin plasma concentrations and greater anticoagulant action (bleeding).

**Factors Affecting Drug Metabolism**

**1. Age:** Neonates and the elderly metabolize some medications less efficiently than adults. The impairment in both situations is caused by decreased activity of hepatic microsomal enzymes. As a result, neonates conjugate chloramphenicol more slowly, resulting in toxicity-grey baby syndrome. The elderly have a higher risk of toxicity with propranolol and lignocaine due to impaired hepatic metabolism.

**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.

1. **Genetic variables (pharmacogenetics):** These factors have an impact on drug metabolism as well. Pharmacogenetics is the study of genetically determined variation in medication response. 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)** Succinylcholine apnoea: Succinylcholine is a neuromuscular blocker that is depolarizing. Plasma pseudocholinesterase enzyme metabolizes it. 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)** Glucose-6-phosphate dehydrogenase (G6PD) deficiency and hemolytic anemia: G6PD activity is required for RBC integrity. 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**

This is the term used to describe a drug's metabolism as it travels from the site of absorption to the systemic circulation. All medications taken by mouth are subject to drug metabolizing enzymes in the liver and intestinal wall (where they initially enter through the portal vein). By giving the medication via sublingual, transdermal, or parenteral routes, presystemic metabolism in the gastrointestinal tract and liver can be prevented. Limited presystemic metabolism, however, can take place in the lungs (for drugs reaching venous circulation via any route) and skin (for drugs delivered transdermally). 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.

1. **Sweat and saliva** These have a negligible impact on drug excretion. Significant levels of lithium, potassium iodide, rifampin, and heavy metals are found in these secretions. The majority of the medicine in the saliva is ingested along with it and has the same outcome as an oral drug.
2. **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:**Through renal arteries, which separate to create a glomerular capillary plexus, drugs are delivered to the kidney. As part of the glomerular filtrate, unbound drugs that are not bound to albumin pass past the capillary slits and into the Bowman space. The glomerular filtration rate (GFR), which is typically around 125 mL/min, may drastically decline in cases of renal illness or be seriously affected in elderly and diabetic people. 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:** Through efferent arterioles, which split to create a capillary plexus around the nephric lumen in the proximal tubule, drugs that were not transported into the glomerular filtrate leave the glomeruli. Two energy-intensive active transport mechanisms, one for anions (such as deprotonated forms of weak acids) and one for cations (such as protonated forms of weak bases), are principally responsible for secretion in the proximal tubules. Each of these transporters may move a wide variety of chemicals and has limited selectivity.

**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:

CLtotal = CLhepatic + CLrenal + CLpulmonary + CLother

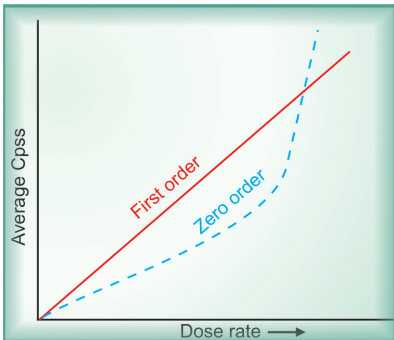
where CLhepatic + CLrenal are typically the most important. Care should be exercised while administering. [2]

**First order kinetics**

A consistent portion of the drug existing in the body is removed in a given amount of time, or the rate of elimination is directly proportional to the drug concentration, CL remains constant. This is true for most medications that do not overwhelm the systems responsible for eliminating 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.

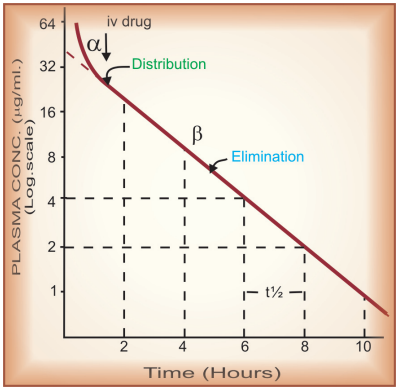
**Plasma half-life**

A drug's plasma half-life (t12) is the amount of time it takes for the plasma concentration to drop to half of what it was initially. A semilog plasma concentration-time plot, as seen in the image, is produced when a drug with a fast one compartment distribution and first order elimination is administered intravenously. 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]

**REFERENCE**

1. Tripathi K.D. (2013)**,** “Essentials of Medical Pharmacology” 7th Edition, Jaypee Brothers Medical Publishers (P) Ltd. New Delhi.
2. Sharma S (2019), “Lippincott® Illustrated Reviews: Pharmacology”, South Asian Edition, N Wolters Kluwer (India) Pvt. Ltd.
3. Rang H P, Ritter J M, Flower R J and Henderson G (2016), “Rang And Dale’s Pharmacology”, 8th Edition, Elsevier Churchill Livingstone.
4. Tara V Shanbhag, “Health Sciences Library “Pharmacology”
5. B Laurence (2006), “Goodman and Gilman’s The Pharmacological Basis of Theapeutics”, 11th Edition, McGraw-Hill.
6. <https://www.onlinebiologynotes.com/membrane-transport-system-passive-active-transport/>