**Pharmacokinetics**

Soubhik Bhattacharyya

Assistant Professor

School of Pharmacy

ARKA JAIN UNIVERSITY Jharkhand, India

[**soubhikbhattacharyya8505@gmail.com**](mailto:soubhikbhattacharyya8505@gmail.com)

Snigdha Rani Behera

Associate Professor

School of Pharmacy

ARKA JAIN UNIVERSITY Jharkhand, India

[**sni\_roldy@yahoo.com**](mailto:sni_roldy@yahoo.com)

GowriSankar Chintapalli

Assistant Professor

School of Pharmacy

ARKA JAIN UNIVERSITY Jharkhand, India

**chintapalli.sankar@gmail.com**

**Abstract**

Pharmacokinetics is the study of how a drug interacts with the body. It focuses on medication absorption, distribution, metabolism and elimination, but it can also be used to assess the time course of endogenous substances and exogenous (environmental) toxicologic agents. The toxicologic pathologist will have a solid foundation from which to comprehend how pharmacokinetics may be useful if they are aware of four basic pharmacokinetic parameters. During the discussion of the non-compartmental and compartmental approaches for determining in vivo PK parameters, an overview of allometric scaling is presented. Brain penetration and intestine absorption are considered in relation to compound permeability. The volume of distribution, plasma protein and tissue binding, as well as systemic, hepatic, renal, and biliary clearance of both small and big molecules, are all covered. How to calculate a metabolite's post-NCE PK parameters is explained in the section on metabolite kinetics. Finally, a section on PK/PD reviews and connects mathematical models used to represent pharmacodynamics (PD), the relationship between the NCE/compound concentration at the site of action and the ensuing impact.

Keywords: pharmacokinetics, compartment model, i.v. Bolus, i.v. Infusion.

1. **Introduction.**

Pharmacokinetics (PK) is an exploration of the way xenobiotics (drugs, chemicals, and NCEs) circulate within the system after being administered, in contrast, pharmacodynamics (PD) is the study of the interaction among a substance's or NCE's concentration at the site of action, the location of the targets for treatment (such as receptors, transporters, or enzymes), and the extent of the therapeutic response. In its most basic form, the distinction between PK and PD can be summarised as follows: the PK describes what the body does to the drug, while PD describes what the drug does to the body [1]. Both domains of inquiry are crucial for determining the pharmacological efficiency and distribution profiles of substances/NCEs in the body [2], and they might be affected depending on experimental and clinical variables (such as gender, species, age, and disease state).

**Dose of drug administered**

**Absorption**

**Distribution**

**Drug in tissue of distribution**

**Drug concentration in systemic circulation**

**Elimination**

**Drug metabolised or excreted**

**Drug concentration at site of action**

**Pharmacological Effects**

**Clinical Responses**

**Toxicity Effectiveness**

**Fig 1: Mechanism of action of the drug in the4 body**

* 1. **Absorption, Distribution, Metabolism and Excretion.**

Absorption and distribution are influenced by physicochemical characteristics. The peak of absorption into the systemic circulation from the site of administration occurs when the drug's concentration in the blood reaches the highest level possible. Typically, chemicals are distributed through dispersion through pores, where they are then exposed to metabolism and removal, primarily by the liver and kidneys, accordingly [2]. Several transporter proteins also participate in the transcellular absorption, distribution, or excretion. An important role in absorption, distribution, and excretion is played by the solute carriers (SLC) and the ATP-binding cassette (ABC) transporters (Drug Metabolism). In that book chapter, it is described how many variables, including those affecting metabolism, play a part in pharmacokinetics, including heredity, disease, age, lifestyle, and diet. Concentration-time profiles after intravenous administration of a substance frequently show a gradual decrease in blood concentrations with a half-life, or t1/2, the amount of time needed for the concentration to fall by half. Following oral administration of the drug, there are different stages of absorption and stages where excretion predominates. Based on the quantity and time of distribution equilibria and release from tissues, substances like the antibiotic gentamicin, which is absorbed into bone, muscle, and kidney, may display multi-compartmental models. For instance, the first phase, or phase, in a two-compartmental model results from both distribution to other body parts and elimination, which causes a fast fall in blood concentration. The second phase, also known as phase 2, is when the body's numerous tissues and fluids are distributed evenly and removal from the body takes centre stage.

**1.2.1 Absorption**

Absorption usually happens after oral delivery through passive diffusion of the unionised form. As a result, the degree of passive absorption is greatly influenced by the pKa or pKb as well as the pH of the immediate surroundings and tissue targeted. Since the stomach has a pH of 2, the ionised form would be preferred. A patient's stomach pH would rise if they were taking an antacid to treat an ulcer, which would result in fewer molecules being ionised and more passive absorption. Other substances might either experience active transport or assisted transfer along a concentration gradient [3]. SLC transporters from the organic cation transporter (OCT) and organic anion transporter (OAT) families are examples of facilitated transport pathways. illustrative substrates for the OAT superfamily include digoxin, rifampicin, penicillin G, salicylate, and quinine and quinidine for the OCT superfamily. Drugs can be pumped back into the lumen by active efflux transporters from the P-glycoprotein (P-gp) family, which limits drug absorption and encourages urine and biliary clearance. Vinca alkaloids like vinblastine, vincristine, vindesine, and vinorelbine are P-gp substrates, which explains why some people are resistant to these drugs. The volume of distribution (VD) might change depending on how transporters are acting. For instance, blocking liver-based efflux and uptake transporters may lessen the risk of VD. It is believed that flavonoids, including iso-orientin, which are found in many plants and have anti-oxidation, anti-inflammatory, anti-cancer, and antidiabetic properties, undergo substantial first-pass metabolism. From the chinese medication danshen (s. miltiorrhiza) it is observed that Intravenous formulations of their less hydrophobic compounds for cardiovascular disorders and angina have been made achievable by the poor penetration and extensive breakdown of the polyphenols and tanshinones. By comparing the proportion of a drug that enters the systemic circulation after oral and intravenous administration, either with a elimination time in between or by giving the intravenous dose as a stable isotope-labeled version, it is essential to understand the bioavailability of an element. This has the added benefit of cutting down on the number of animals needed, cutting down on the amount of time it takes to conduct the studies, and doing away with the need for a washout interval in between doses when it is done in animal trials. An example of a substance that can be dosed via many channels is Artemisin, an antimalarial phytochemical isolated from Artemisia annua. It can be administered intravenously, intramuscularly, orally, or via rectal route. Artemisin has a 30% bioavailability when taken orally due to first-pass metabolism. Morphine is an additional natural substance that has a sizable first-pass effect and is consequently delivered intravenously. Because it breaks down in the stomach's acid, Penicillin G cannot be used orally. Large compounds like mistletoe leptins and quaternary amines, which are employed in supportive cancer treatment but must be injected because they cannot be absorbed, include the muscle relaxant tubocurarine from Chondrodendron tomentosum. Conopeptides, like the analgesics Ziconotide and Contulakin-G from Conus geographus, are big, charged molecules that are difficult to pass across membrane barriers and are broken down by peptidases after being administered orally or intravenously [4]. In order for these labile chemicals to work, they must be delivered intrathecally into spinal fluid. The carrier substance can be changed to increase oral bioavailability. The creation of a "phytosome," in which the active components of the plant are attached to phospholipids with one hydrophilic head and two hydrophobic tails, is a common strategy for lipid-soluble pharmaceuticals. Ginkgo biloba, milk thistle, grape seed, green tea, hawthorn, and ginseng formulations have all used this. The bio availabilities of hyperforin and hypericin, the active ingredients in Hypericum perforatum (St. John's Wort), have been effectively increased by about threefold when lipophilic soft-capsules of gelatin with the natural surfactant lecithin were used instead of commercial hard-shell capsules without surfactant. Parallel to it, Silipide, a lipophilic silybinphospatidylcholine complex, was created to increase the oral bioavailability of silybin from milk thistle. When given as a phospholipid complex rather than in their free form, Ginkgolide A, B, and Bilobalide from G. bilboa extracts nearly doubled in maximum plasma concentrations. To increase solubility and absorption, studies on oligoethylene glycol chains, membrane carriers, and lipophilic derivatives of natural compounds have been conducted. Additionally, pH-sensitive nanoparticles have been created for drugs such andrographolide from Andrographis paniculata to boost bioavailability while limiting drug delivery to the tumour. Compound absorption can be predicted using in vitro research, such as Caco-2 permeability models. A colorectal epithelial adenocarcinoma cell line from a patient is included in this model. The octanolwater partition coefficient, molecular weight (MW), number of hydrogen-bond donors and acceptors, and number of hydrogen-bond acceptors all affect the absorption in different ways. A chemical violates Lipinski's "rule of 5" if its logP is higher than 5, its MW is higher than 500, there are more than 10 hydrogen bond acceptors, or there are more than 5 hydrogen bond donors. A chemical is likely to have poor absorption or penetration if it contains two or more violations. The compounds with both a fatty acid chain and a benzene group, such as yuanhuafine and yuanhuapine, were poorly absorbed of all the components of Daphne genkwa, a Traditional Chinese Medicine used for its diuretic, antitussive, expectorant, abortifacient, and antitumor properties.

**1.2.1.1 Factors affecting Absorption**

**Influence of pH**

When a lipid soluble drug is consumed, absorption is enhanced. The degree of ionisation and rate of medication absorption are influenced by the pH of the surrounding medium for weak electrolytes. The two structures appear to have qualitatively different patterns of medication absorption because the H+ concentrations in the small intestine and stomach differ greatly. Aspirin is an organic acid with a pKa (negative log of the dissociation constant) of 3.49, which is used in the scenario to demonstrate the impact of pH [5]. Aspirin is generally nonionized in gastric acid (pH 1 to 3), which facilitates its transit through the stomach mucosa and into the bloodstream. However, the aspirin becomes so highly ionised in the plasma, which has a pH of 7.4, that the low lipid solubility of the anionic species prevents the drugs from returning to the gastrointestinal system. The concentration of nonionized aspirin molecules is the same on both sides of the membrane when equilibrium is reached, but the total amount of drug (ionised plus neutral forms) is significantly higher on the plasma side. Using the Henderson-Hasselbalch equation, the relative drug concentration in each compartment can be computed as follows:

Ion trapping is demonstrated by the disparate distribution of the drug molecules across the stomach membrane based on the pH gradient. The biological process that keeps this partitioning going is the stomach parietal cells' energy-intensive release of H+. Nearly all acidic medications could theoretically be adequately absorbed through the gastric mucosa since few organic acids have a pKa adequate to permit considerable ionisation at stomach pH. On the other hand, this is not true for bases like codeine (pKa 7.9). The acidic condition of the stomach causes codeine to almost entirely ionise; little of the drug is absorbed outside of the stomach. At stomach pH, only extremely weak bases become nonionized and absorbable. In this instance, ion trapping takes place in the stomach lumen prior to absorption. (Interestingly, forensic medicine occasionally finds use for this. Intoxicating substances with organic basis include heroin, cocaine, and amphetamine. Chemicals often accumulate in the stomach by penetrating the gastric membrane in the opposite way, even when administered intravenously. The study of stomach contents can frequently provide answers to questions about intravenous overdosage.) Pancreatic, biliary, and intestinal secretions immediately neutralise the acidic stomach fluid as soon as it enters the small intestine. The proximal quarter of the intestine's pH ranges from 3 to 6, while more distant regions are where it reaches neutrality. Aspirin changes to the anionic form in these more alkaline conditions, whereas a sizable portion of the molecules of codeine lose their positive charge. Because of the minor pH difference across the intestinal mucosa, basic medicines are preferred for absorption over acids in the small intestine, but ion trapping is not as extensive. Intestinal absorption variations based on pH are more concerned with uptake's rate than its extent. As one might anticipate, the qualitative difference in electrolyte absorption often observed between the stomach and the small intestine is momentarily eliminated by neutralising gastric contents by the injection of antacids or intake of food.

**Mucosal surface area**

The intraluminal surfaces responsible for drug uptake constitute a second important distinction between absorption in the small intestine and absorption in the stomach. With the exception of a few mucosal imperfections called rugae, the stomach's lining resembles a smooth pouch covered in a thick mucus layer. The mucosa of the small intestine, on the other hand, is especially suited for absorption. The Kerckring folds, villi, and microvilli all contribute to a 600-fold increase in the effective surface area. A tiny intestine with a diameter of 4 cm and a length of 280 cm would have 200m2 accessible for medication absorption. Because of the small intestine's high surface-to-volume ratio, medications that have been ionised up to 99% of the way may still be successfully absorbed. Numerous investigations have demonstrated that basic substances with pKa values lower than 8.0 and acidic medications with pKa values higher than 3.0 easily move from the intestinal fluid into the plasma. As a result, even if pH factors favour aspirin absorption in the stomach, up to 90% of the medication is actually absorbed in vivo from the small intestine. According to experimental data, non-electrolytes like ethanol are absorbed from the intestines far more quickly than they are from the stomach.

**Gastric emptying**

The timing of gastric emptying can have a considerable impact on drug absorption because practically all substances that can pass the gastrointestinal epithelium are better absorbed in the small intestine, especially for organic bases that are not absorbed at all from the stomach. The contraction of the stomach's antrum causes the stomach to empty. In fasting patients, there is a cyclical pattern of activity, with periods of quiescence lasting approximately an hour apiece, followed by contractions that get stronger over the course of 40 minutes, ending in a brief burst of severe contractions that go from the stomach to the distal ileum. A tablet or little number of fluids may cause the medicine to be retained in the stomach for up to an hour. Prolonged antral and pyloric contractions after a meal aid in breaking up the ingested food and allow fluids to be expelled into the duodenum while keeping food particles larger than 1 mm in diameter inside the stomach. An average meal that contains both liquids and solids starts to reach the duodenum in about 30 minutes and takes about 4 hours to completely depart the stomach. On the other hand, a glass of water consumed on an empty stomach is transported into the small intestine more quickly, with half of the liquid leaving the stomach in 15 minutes and almost all of it by an hour later. The presence of fat is a key factor in slowing down stomach emptying. The majority of oral drugs should typically be taken without meals and with a full glass of water. This method maximises access to the gastrointestinal mucosa while hastening medication entrance into the small intestine. On occasion, a fatty meal can aid in the absorption of a medication with a high lipid content but poor water solubility. Examples of compounds that are better absorbed in the presence of lipids include the fat-soluble vitamins and the protease inhibitor saquinavir. In these cases, a more thorough absorption makes up for the delayed stomach emptying brought on by the chyme's high fat content. Since the pace of medication absorption is frequently constrained by gastric emptying, many unrelated drugs have latency periods (the interval between oral administration and the start of a drug's effects) of comparable length.

**Influence of dosage form**

Although the durations needed for gastric emptying and mucosal barrier diffusion surely play a role in the delayed beginning of action of medications taken orally, there are some circumstances where these events are not rate limiting. The majority of medications offered for oral use come in the shape of capsules or solid tablets. These medications have to dissolve within the gastrointestinal fluid, as opposed to solutions, before absorption can take place. Dissolution may become the deciding factor in drug absorption if it is intended to dissolve very slowly. The tablet (or the capsule and its granules) must be broken down in order to release the principal drug particles during the dissolution process. When a medication solution delivers a systemic impact more quickly than a solid formulation of the same agent, the dissolution process may be seen as rate-limiting. There are times when there are significant changes in how different dosage forms are absorbed, leading to clinical differences. When taking aspirin, a solution may result in a drug concentration in the blood 30 minutes after delivery that is twice as high as a solid tablet. Dissolution is probably at least largely to blame, even if it is uncertain whether this variation is the sole result of medication dissolution or perhaps other factors, such as the quicker stomach emptying that is typical of liquids. Pharmaceutical manufacturers frequently exploit the impact of dose type on drug absorption. They are frequently manufactured in the form of enteric-coated tablets to prevent the release of some medications in the stomach. A film made of shellac or another polymeric replacement makes up an enteric coat. Under acidic conditions, the covering is insoluble, but it does disintegrate to allow tablet breakdown in the small intestine's more alkaline environment. Despite the fact that these preparations are frequently helpful, the greater unpredictability in patient response has a detrimental impact on their efficacy. The time it takes for the tablet to move through the stomach into the duodenum is a crucial factor since drug absorption cannot start until the tablet enters the duodenum. A single insoluble tablet's random journey from the stomach to the intestine can take anywhere from a few minutes to more than 6 hours. Another strategy for maximising the impact of formulation on drug absorption is the use of sustained-release formulations. These products are often made to distribute a constant dosage of medication into the digestive system for 12 to 24 hours. A rapidly absorbable first loading dose is also offered by some formulations. Using a porous matrix and placing the drug in the internal spaces and on the exterior surface can achieve sustained release. Making drug-filled spheres with varying coatings that dissolve at various rates is an alternative. The issue of bioavailability is the best illustration of how sensitive gastrointestinal absorption is to changes in drug composition. Because of variations in formulation, chemically identical medications have frequently shown to be biologically non-equivalent in the past. Nine formulations of the medicine, made by several manufacturers, were compared to an aqueous solution in one investigation on tetracycline hydrochloride. Even though blood concentrations for seven brands ranged from 70% to 100% of the reference solution, only 20% to 30% of the reference solution was relative bioavailable for two items. With medications that are poorly absorbed, have small margins of safety, and dissolve by capacity-limited mechanisms, variations in bioavailability are more clinically significant.

* + 1. **Distribution**

Similar to absorption, the distribution of xenobiotics is influenced by a variety of physicochemical characteristics of the molecule, including its MW, degree of ionisation, and lipophilicity. For instance, theophylline has a lesser tissue distribution of the methylxanthine than caffeine, which is more lipid soluble. One element that can lessen the breadth of blood distribution to distant places is plasma protein binding. While basic medications bind to locations on -globulin and 1-acid glycoprotein, acidic drugs mostly bind to albumin. A bigger portion of the amatoxins found in the Amanita, Galerina, and Lepiota genera of mushrooms can circulate throughout the body because they lack protein binding characteristics. On the other hand, the proteinbound fraction of paclitaxel (taxol), an anticancer medicine derived from the bark of the Pacific Yew, Taxus brevifolia, is 0.890.98. Camphor, which has a moderate lipophilicity and is volatile, exhibits intermediate plasma binding, with a bound fraction of 0.61. As with polyphenols in Type II diabetes, when excess glucose competes with polyphenols for binding to plasma proteins, illness can affect plasma binding. Additionally, the noncovalent interactions between plasma proteins and polyphenols are weakened by protein glycation. Different compounds may exhibit varying degrees of dispersion in red blood cells. Tetrahydrocannabinol concentrations in plasma, for instance, are almost two times higher than those in whole blood, and a larger amount is available for distribution because very little of it is transported into red blood cells. Compartmental models are frequently used to define distribution. Two compartments might exist, for instance, if a tissue or fluid's concentration is reduced and this is followed by a rise in the number of other tissues that are in equilibrium with one another. In humans, andrographolide, an antiviral drug derived from Andrographis paniculata, displays a two-compartmental model. The same substance can display one- and two-compartmental models in several subjects when given at the same dose. Four of the 15 participants who received andrographolide showed one-compartmental models, while the remaining 13 showed two-compartmental models. The time allotted for sampling affects how many compartments are chosen. For instance, the three-compartmental models of vincristine, vinblastine, and vindesine only become apparent when plasma concentrations are tracked longer for 48 hrThe circulating blood has an average volume of 5 L, with a plasma volume of about 3 L, which is where the compounds are distributed. A typical adult contains about 42 L of water total, of which 25 L are considered intracellular fluids and the remaining fluids, including plasma, are extracellular. The degree of dispersion throughout the body is indicated by the apparent VD in L/kg. Low VD substances frequently exhibit high plasma protein binding and an increased potential for competition compared to those with high blood concentration. Due to their great tissue-binding abilities, individuals with a high VD have low blood concentrations. The apparent VD is adjusted when a substance is taken orally through multiplying by the bioavailability. In many cases, the bioavailability is unclear, and apparent VD is represented by the symbol VD/F. The majority of substances have a VD of between 0.1 and 10 L/kg, or 40 to 0.4%, respectively, of the total body water compartment. Digoxin has a low therapeutic concentration of 0.92 ng/mL due to its high VD of 5.17.4 L/kg. Due to the lack of a single hydroxyl moiety, digitoxin, which is generated from the same plant and chemically very similar, has a VD of 41 L/kg. Galantamine, a medication with a high VD due to its low protein binding and high bioavailability, is derived from the daffodil genera Galanthus and Narcissus and is used to treat degenerative dementias like Alzheimer's. Numerous substances show preferential distribution to specific organs. For instance, traditional Chinese medicine uses puerarin, which is produced from the root of the kudzu plant Pueraria lobota, to treat people with cardiovascular, neurological, and hyperglycemic diseases. Its distribution into the kidney and pancreas in rat models supports its role in enhancing the diabetic state [6]. However, the lung was shown to have the largest quantities, thus attempts are currently being made to determine the advantages of this organ. Lipophilic compounds with the potential to treat different malignancies include camptothecin and 10-hydroxycamptothecin, indole alkaloids from Camptotheca acuminate, which are transported into tumour cells, kidneys, bone marrow, and enterohepatic system in mice. Antimalarial artemisinin preferentially distributes to the gut in rats, followed by the brain, kidney, and liver. Despite making up only 0.8% of total body weight, 8.1% of the amount of the antioxidant contained in olive oil called hydroxytyrosol that was delivered was discovered in the kidney 5 minutes after administration. In animal models, it has been demonstrated that the animal toxin tetrodotoxin from the Tetraodontidae species, such as the Japanese puffer fish, is readily absorbed after subcutaneous injection but concentrates in the liver and kidneys within 2 hours. Lipophilic compounds from Camptotheca acuminate, such as 10-hydroxycamptothecin and camptothecin, are transported into tumour cells, kidneys, bone marrow, and the enterohepatic system in mice. There is some evidence to suggest that giving natural products in the form of a phospholipid complex enhances tissue dispersion. For instance, when given as a compound with a soy phospholipid, the Chinese drug puerarin shows increased tissue distribution in the heart, lung, and brain. Targeting natural products to specific tissues has been accomplished via a variety of additional techniques. For instance, the creation of natural product-antibody conjugates has been a key component of tumor-targeted therapy. A monoclonal antibody that recognises the glycoprotein seen on human melanoma cells was linked to the ribsome inactivating protein gelonin in mice to demonstrate the effect.

**1.2.3 Metabolism**

Along with to more moderate routes like carboxylation, cyclization, isomerization, dimerization, and transamidation, phase I reactions also include oxidation (for example, hydroxylation, dealkylation, and deamination), reduction, hydrolysis, or hydration. Certain metabolites are important because of their action. For instance, a pharmacologically active metabolite of the antineoplastic vinblastine is produced through deacetylation. Plasma esterases, in addition to liver enzymes, are involved in the breakdown of narcotics like heroin and cocaine. Bacterial metabolism and anaerobic metabolic processes including hydrolysis and reduction take place in the mucosal lining of the digestive tract. Flavonoids are broken down into phenolic acids by bacteria and hydrolyzed by lactase phlorizin hydrolase. Semisynthetic analogues can be modified to provide different half-lives for substances with suboptimal metabolism that cause prolonged or diminished activity. For instance, the semisynthetic analogue, everolimus, has a half-life of 30 h compared to 60 h for the cancer medication sirolimus. Phase II reactions include glycosidation, methylation, acetylation, amino acid and glutathione conjugation, and glucuronide, sulphate, and amino acid reactions. Although morphine-6-glucuronide has been proven to be an active metabolite, most glucuronide conjugates are inactive. Through the action of uridine 5'-diphospho-glucuronosyltransferases (UGTs), sulfotransferases, efflux transporters, and deconjugation by microbial enzymes, glucuronide conjugates can be recirculated throughout the body by enterohepatic circulation, resulting in prolonged drug activity and excretion. For instance, the pharmacologically active components of the Traditional Chinese Medicine combination of Coptidis rhizoma and Evodiae fructus, berberine, palmatine, and jatrorrhizine, showed three peaks in a time concentration profile in animal studies, indicating repeated recycling of these compounds into other substances.

* + 1. **Excretion**

The kidney filters the majority of substances, which are then expelled from the body through the urine or faeces. Filtration, secretion, and tubular reabsorption are the three main methods of renal excretion. In young, healthy people, the average renal nephron filters 100–130 mL of blood per minute. It is clear for weak bases and acids with pKa and pKb values in the physiological pH range that tubular reabsorption is pH-dependent. The urine's pH changes with eating and ranges from 4.5 to 7.5. As a result, when the ionised water-soluble forms predominate, salicylic acid is more likely to be discharged into alkali pee and morphine in acidic urine. Alkali diuresis can be used to control excretion using a sodium bicarbonate injection. For instance, alkalinization causes a lesser proportion of ephedrine to be excreted (2235%), as well as more norephedrine (1124%) and around 7080% of ephedrine to be excreted unmodified and 4% as norephedrine. Contrarily, filtration is dependent on MW, making protein-bound medicines and substances with MWs greater than 500 inapplicable. Through a variety of uptake and efflux transporters, certain ions are vulnerable to active tubular secretion into the kidney from the blood in the proximal convoluted tubule of the kidney. For instance, carrier-mediated processes are involved in penicillin secretion [7]. The idea behind combining it with probenicid to extend the effects of penicillin is that other weak acids are also able to compete for the carrier protein. For instance, ephedrine is normally eliminated in the urine in around Additionally released by OATs are salicylates and glucuronide metabolites, while cation transporters secrete morphine. Due to tubular secretion, atropine has a high renal clearance. The conjugation and intestinal deconjugation of biliary excretion can lead to enterohepatic circulation, which is a significant route of elimination. Digoxin, antibiotics, and quercetin have all been studied using invasive methods on healthy human volunteers to directly see biliary excretion. Transporters from the ABC B (BSFP and MDR1) and ABC C (MRP1 and 2) families are involved in biliary excretion. Escin, an anti-inflammatory combination of triterpenic saponins found in horse chestnut (Aesculus hippocastanum) seeds, is an example of a substance that, in animal models, is primarily (66% of the dose) excreted into bile. Up to 20% of morphine-3-glucuronide in rat models is excreted into the bile, and the transporter MRP 3 has been linked to this process. In rodents, dogs, and people, vinca alkaloids such vinblastine, vincristine, vindesine, and vinorelbine are excreted in the bile and faeces. Deactivation during metabolism requires removing the endoperoxide structure, predominantly via CYP 2B6. Although the metabolites have been found, the mechanism has not yet been determined. When a substance exhibits first-order kinetics, the rate of elimination is expressed using the t1/2. Some medications contain a number of different chemicals with various half-lives. For instance, the Chinese medicinal Shakuyakukanzoto, which contains Glycyrrhizae (liquorice) and Paeoniae (peony) and is used to treat muscle cramps, has substances with half-lives that range from 1.7 hours (paeoniflorin) to 15 hours (glycycoumarin). As a result, a drug is created that has the simultaneous rapid and long-lasting ability to relieve muscle cramps and maintain analgesia, thanks to the synergistic interactions between at least six different pharmacokinetic components. Clearance, which is frequently given in units of mL/min/kg, is the amount of blood or plasma that is cleared of drugs per unit time by all clearing organs. It is used to describe how the liver, kidneys, and other cleaning organs metabolise and excrete substances. The extraction ratio, E, of a specific organ, which is the percentage of compound eliminated from the plasma by the organ during its passage through the organ, determines the clearance of that organ. E is a result of metabolic enzyme or transporter activity, protein binding, and organ blood flow. The total body clearance is calculated as the sum of the clearances of each organ. Clearance is sometimes stated as a fraction of the VD to indicate persistence in the body (CL/VD), a word that is also an expression of the elimination rate constant, because a molecule with a large VD will persist in the body. A high renal clearance would suggest vigorous secretion, filtration, and a relatively low rate of reabsorption. For substances that are extensively metabolised in the liver, a high hepatic clearance would be anticipated.

* 1. **The Pharmacokinetic applications.**

**Design of dosage regimens:**

A dose regimen can be created using a variety of techniques. Typically, the initial dosage of the medication is calculated using the standard population pharmacokinetic parameters that are taken from the literature and modified in accordance with the patient's known diagnosis, pathophysiology, demographics, allergy, and any other known factors that might affect the patient's response to the dosage.

The dosing strategies are typically based on manually completed pharmacokinetic calculations.

The calculation accuracy is increased, the calculations are made "easier," and there is an added benefit of maintaining a good documentation schedule with computer automation and pharmacokinetic software packages.

* **Nomograms and Tabulations in designing dosage regimen,**
* The initial pharmacokinetic variables for drug dosing in particular patients for whom patient-specific parameters are unknown are frequently estimated using nomograms or equations that describe the relationships between patient characteristics (e.g., age, weight, gender, disease states, interacting drugs, environmental factors-smoking & food) and pharmacokinetic parameters in a population.
* **Tabulation:**

The tables may include loading and maintenance doses that are modified for the demographics of the patient (eg, age, weight) and for certain disease states (eg renal insufficiency).

* **Conversion from intravenous to oral dosing,**
* **Determination of dose and dosing intervals,**
* **Drug dosing in the elderly and pediatrics and obese patients.**

**Pharmacokinetics of Drug Interaction:**

It is the process whereby the prior concurrent administration of one medicine (the precipitant drug) modifies the impact of another (the object drug). The use and security of many medications can be significantly impacted by metabolism-based drug interactions and other factors.

Drug concentrations may unexpectedly decline or metabolite concentrations may increase when drug metabolism is induced. When drug metabolism is inhibited, the opposite can happen.

The liver is the primary organ involved in metabolism, and CYP450, a well-known family of oxidative hemo-proteins, is the primary enzyme system involved in drug metabolism. The liver's CYP 450 enzyme induction is what triggers the metabolism of many medications.

Inhibition:

The phenomenon of decreased drug metabolizing ability of the enzymes by several drugs and chemicals is called as enzyme inhibition. The process of inhibition may be of two types:

[1]. Direct Inhibition

[2]. Indirect Inhibition

Induction:

The phenomenon of increased drug metabolizing ability of the enzymes by several drugs and chemicals is called as enzyme induction.

A number of drugs can cause an increase in liver enzyme activity over time. This in turn can increase the metabolic rate of the same or other drugs. Phenobarbitone will induce the metabolism of itself. Phenytoin, warfarin, etc.

**Therapeutic Drug monitoring:**

The idea that pharmacologic response is closely connected to drug concentration at the site of action underlies the utility of plasma drug concentration data. Studies on individuals have revealed the plasma concentration range for several medications that is safe and efficient in treating particular disorders. The intended effects of the medication are observed within this therapeutic range. If it is below it, there is a higher chance that the therapeutic advantages will not be experienced; if it is over it, harmful repercussions could happen.

Therapeutic drug monitoring is the process of using assay techniques to measure drug concentrations in plasma and interpreting and applying the concentration data obtained to create treatment regimes that are both safe and effective. faster and more safely than is possible with empiric dose adjustments, therapeutic concentrations of a medication can be reached. The safest method for achieving ideal drug therapy should be provided, together with observations of the medicine's clinical effects.

**Individualization of drug dosage regimen (Variability – Genetic, Age and Weight, disease, Interacting drugs).**

Not all drugs require rigid individualization of the dosage regimen. Many drugs have a large margin of safety (i.e., exhibit a wide therapeutic window), and strict individualization of the dose is unnecessary. The U.S. Food and Drug Administration (FDA) has approved an over-the-counter (OTC) classification for drugs that the public may buy without prescription. In the past few years, many prescription drugs, such as ibuprofen, loratidine, omeprazole, naproxen, nicotine patches, and others, have been approved by the FDA for OTC status. These OTC drugs and certain prescription drugs, when taken as directed, are generally safe and effective for the labeled indications without medical supervision.

For drugs with a narrow therapeutic window, such as digoxin, aminoglycosides, antiarrhythmics, anticonvulsants, and some antiasthmatics, such as theophylline, individualization of the dosage regimen is very important.

* **Indications for TDM and Protocol for TDM.**
* **Pharmacokinetic/Pharmacodynamic Correlation in drug therapy.**
* **TDM of drugs used in the following disease conditions: cardiovascular disease, Seizure disorders, Psychiatric conditions, and Organ transplantations**

**Dosage adjustment in Renal and hepatic Disease.**

* **Renal impairment**
* **Pharmacokinetic considerations**
* **General approach for dosage adjustment in Renal disease.**
* **Measurement of Glomerular Filtration rate and creatinine clearance.**
* **Dosage adjustment for uremic patients.**

Nomograms are charts available for use in estimating dosage regimens in uremic patients The nomograms may be based on serum creatinine concentrations, patient data (height, weight, age, gender), and the pharmacokinetics of the drug. As discussed by Chennavasin and Brater (1981), each nomogram has errors in its assumptions and drug database.

Most methods for dose adjustment in renal disease assume that nonrenal elimination of the drug is not affected by renal impairment and that the remaining renal excretion rate constant in the uremic patient is proportional to the product of a constant and the Cler

ku = knr + a Cler

where knr is the nonrenal elimination rate constant and a is a constant.

Equation is similar to next Equation, where 1/VD, and it can be used for the construction of a nomogram.

* **Extracorporeal removal of drugs.**
* **Effect of Hepatic disease on pharmacokinetics.**

**Population Pharmacokinetics.**

Population pharmacokinetics (Pop-PK) is the study of variability in plasma drug concentrations between and within patient populations receiving therapeutic doses of a drug.

* **Introduction to Bayesian Theory.**

Bayesian theory was originally developed to improve forecast accuracy by combining subjective prediction with improvement from newly collected data. In the diagnosis of disease, the physician may make a pre-liminary diagnosis based on symptoms and physical examination.

Later, the results of laboratory tests are received. The clinician then makes a new diagnostic forecast based on both sets of information. Bayesian theory provides a method to weigh the prior information (e.g., physical diagnosis) and new information (e.g., results from laboratory tests) to estimate a new probability for predicting the disease.

* **Adaptive method or Dosing with feed-back.**

In dosing drugs with narrow therapeutic ratios, an initial dose is calculated based on mean population pharmacokinetic parameters.

After dosing, plasma drug concentrations are obtained from the patient. As more blood samples are drawn from the patient, the calculated individualized patient pharmacokinetic parameters become increasingly more reliable. This type of approach has been referred to as adaptive or Bayesian adaptive method with feedback when a special extended least-squares algorithm is used.

* **Analysis of Population pharmacokinetic Data**
  1. **Rates and orders of reactions.**

Following administration, a drug is put through a series of processes (ADME) whose rates regulate the concentration of the drug in the illusive area known as the "site of action." These mechanisms have an impact on the pharmaceutical response's length, intensity, and point of initial action [4]. Therefore, understanding these rate processes is crucial for comprehending the observed pharmacological action of the delivered drug. Let's use the symbol Y to represent a function that varies over time (t). As a result, time (t) is an independent variable and Y is a dependent variable. The dependent variable (Y) in this chapter can be either the mass of the drug in the body (X), the mass of the drug in the urine (Xu), or the concentration of the drug in the plasma or serum (Cp or Cs, respectively). There will be a very slight change in the value of Y during a very brief period of time, as seen below:

=

where dY/dt is the instantaneous rate of change in function Y with respect to an infinitesimal time interval (dt).

Order of a process In the equation = KYn, the numerical value (n) of the exponent of the substance (Y) undergoing the change is the order of the process.

Typical orders and types of process encountered in science include:

* zero order
* first order
* second order
* third order
* reversible
* parallel
* consecutive

Zero- and first-order processes are most useful for pharmacokinetics.

*X*  Ko  *Product (b)*

where X is a substance undergoing a change

*X*  Ko *X (in another location)*

where X is a substance undergoing transfer

Fig 2: Process of change (zero order).

Zero-order process shows the process of change in a zero-order process. The following is the derivation of the equation for a zero-order elimination process:

=  (1)

where K0 is the zero-order rate constant and the minus sign shows negative change over time (elimination).

Since Y0 = 1,

= K0  (2)

This equation clearly indicates that Y changes at a constant rate, since K0 is a constant (the zero-order rate constant). This means that the change in Y must be a function of factors other than the amount of Y present at a given time. Factors affecting the magnitude of this rate could include the amount of enzymes present, light or oxygen absorbed, and so on.

The integration of Eq. 1 yields the following:

(3)

where Y is the amount present at time t and Y0 is the amount present at time zero. (For example, Y0 could stand for (X)t=0, the mass of drug in the body at time zero. In the case of an intravenous injection, (X)t=0 would be equal to X0, the administered dose.)

X(mg) Slope = -K

time (hr)

Fig 3: Rectilinear graph (R.L.) of zero-order process. X, concentration of drug; K, rate constant.

Equation 3 is similar to other linear equations (i.e., y = b -mx, where b is the vertical axis intercept and m is the negative slope of the line) (Fig. 3).

Applications of zero-order processes

Applications of zero-order processes include administration of a drug as an intravenous infusion, formulation and administration of a drug through controlled release dosage forms and administration of drugs through transdermal drug delivery systems. In order to apply these general zero-order equations to the case of zero-order drug elimination, we will make the appropriate substitutions for the general variable Y. For example, substitution of X (mass of drug in the body at time t) for Y in Eq. 2 yields the zero-order elimination rate equation:

= K0 (4)

Whereas, the counterpart of the integrated Eq. 3 is X = Xt0 – K0t, or

(5)

where Xt=0 is the amount of drug in the body at time zero. (For an intravenous injection, this equals the administered dose, X0.)

Unit of the rate constant (K0) for zero-order elimination of drug

Since dX in Eq. 4 has units of mass and dt has units of time, K0 must have units of mass/time (e.g., mg h-1). This can also be seen by the integrated Eq. 5: Therefore,

**First-order process**

Figure 4 shows the process of change in a first-order process.

*X*  k  *Product (b)*

where X is a substance undergoing a change

*X*  k  *X (in another location)*

where X is a substance undergoing transfer

Fig 4: Process of change (First order).

The following is the derivation of the equation for a first-order elimination process, since the negative sign indicates that the amount of Y is decreasing over time.

= (6)

where Y is again the mass of a substance undergoing a change or a transfer, and K is the firstorder elimination rate constant.

However, since by definition Y1 = Y,

= (7)

Equation 7 tells us that the rate at which Y changes (specifically, decreases) depends on the product of the rate constant (K) and the mass of the substance undergoing the change or transfer. Upon integration of Eq. 7, we obtain:

(8)

(9)

or (10)

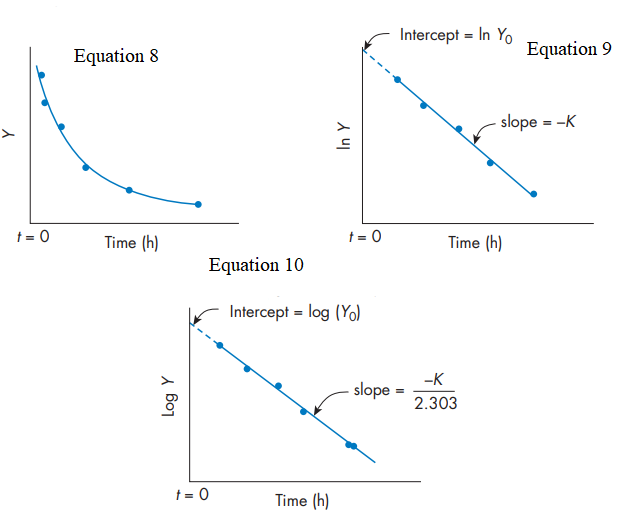


Fig 5: One-compartment intravenous bolus injection: three plots using rectilinear (R.L.) co-ordinates. K, rate constant; Y can stand for mass of drug in the body (X), concentration of drug in plasma, etc

The above three equations for a first-order process may be plotted on rectilinear co-ordinates (Fig 5). Use of semi-logarithm paper (i.e. S.L. plot): Eq. 8 may be plotted (Y versus t) on semilogarithmic coordinates. It will yield a vertical axis intercept of Y0 and a slope of K/2.303 (Fig. 1.18).

Applications

First-order elimination is extremely important in pharmacokinetics since the majority of therapeutic drugs are eliminated by this process.

We apply the general first-order equations above to the case of first-order drug elimination by making the appropriate substitutions for the general variable Y. For example, substitution of X (mass of drug in the body at time t) for Y in Eq. 6 yields the first-order elimination rate equation:

(11)

Upon integration of Eq. 11, we obtain:

(12)

where X0 is the dose of intravenously injected drug (i.v. bolus), or

(13)

or (14)

Unit for a first-order rate constant, K Eq. 11

= K0

or d*X*/dt x *X-*1 = K, where units are mg h-1 x mg-1. So, K has units of h-1.

1. **Pharmacokinetic Models.**

After administering a dose, the change in drug concentration in the body with time can be described mathematically by various equations, most of which incorporate exponential terms (i.e. e x or e x). This suggests that ADME processes are ‘‘first order’’ in nature at therapeutic doses and, therefore, drug transfer in the body is possibly mediated by ‘‘passive diffusion.’’ Therefore, there is a directly proportional relationship between the observed plasma concentration and/or the amount of drug eliminated in the urine and the administered dose of the drug [4]. This direct proportionality between the observed plasma concentration and the amount of drug eliminated and the dose administered yields the term ‘‘linear pharmacokinetics’’. Because of the complexity of ADME processes, an adequate description of the observations is sometimes possible only by assuming a simplified model; the most useful model in pharmacokinetics is the compartment model. The body is conceived to be composed of mathematically interconnected compartments.

* 1. **Compartmental Models.**

The compartment concept is utilized in pharmacokinetics when it is necessary to describe the plasma concentration versus time data adequately and accurately, which, in turn, permit us to obtain accurate estimates of selected fundamental pharmacokinetics parameters such as the apparent volume of drug distribution, the elimination half life and the elimination rate constant of a drug. The knowledge of these parameters and the selection of an appropriate equation constitute the basis for the calculation of the dosage regimen (dose and dosing interval) that will provide the desired plasma concentration and duration of action for an administered drug. The selection of a compartment model solely depends upon the distribution characteristics of a drug following its administration. The equation required to characterize the plasma concentration versus time data, however, depends upon the compartment model chosen and the route of drug administration. The selected model should be such that it will permit accurate predictions in clinical situations [3]. As mentioned above, the distribution characteristics of a drug play a critical role in the model selection process. Generally, the slower the drug distribution in the body, regardless of the route of administration, the greater the number of compartments required to characterize the plasma concentration versus time data, the more complex is the nature of the equation employed. On the basis of this observation, it is, therefore, accurate to state that if the drug is rapidly distributed following its administration, regardless of the route of administration, a one-compartment model will do an adequate job of accurately and adequately characterizing the plasma concentration versus time data. The terms rapid and slow distribution refer to the time required to attain distribution equilibrium for the drug in the body. The attainment of distribution equilibrium indicates that the rate of transfer of drug from blood to various organs and tissues and the rate of transfer of drug from various tissues and organs back into the blood have become equal. Therefore, rapid distribution simply suggests that the rate of transfer of drug from blood to all organ and tissues and back into blood have become equal instantaneously, following the administration (intra- or extravascular) of the dose of a drug. Therefore, all organs and tissues are behaving in similar fashion toward the administered drug Slow distribution suggests that the distribution equilibrium is attained slowly and at a finite time (from several minutes to a few hours, depending upon the nature of the administered drug) [11]. Furthermore, it suggests that the vasculature, tissues and organs are not behaving in a similar fashion toward this drug and, therefore, we consider the body to comprise two compartments or, if necessary, more than two compartments. Highly perfused systems, such as the liver, the kidney and the blood, may be pooled together in one compartment (i.e. the central compartment: compartment 1); and systems that are not highly perfused, such as bones, cartilage, fatty tissue and many others, can also be pooled together and placed in another compartment (i.e. the tissue or peripheral compartment: compartment 2). In this type of model, the rates of drug transfer from compartment 1 to compartment 2 and back to compartment 1 will become equal at a time greater than zero (from several minutes to a few hours). It is important to recognize that the selection of the compartment model is contingent upon the availability of plasma concentration versus time data.

**Transfer**

**Region of low concentration**

**Concentrated Solution**

Therefore, the model selection process is highly dependent upon the following factors.

1. The frequency at which plasma samples are collected. It is highly recommended that plasma samples are collected as early as possible, particularly for first couple of hours, following the administration of the dose of a drug.

2. The sensitivity of the procedure employed to analyse drug concentration in plasma samples. (Since inflections of the plasma concentration versus time curve in the low concentration regions may not be detected when using assays with poor sensitivity, the use of a more sensitive analytical procedure will increase the probability of choosing the correct compartment model.)

3. The physicochemical properties (e.g. the lipophilicity) of a drug. As mentioned above, only the distribution characteristics of a drug play a role in the selection of the compartment model. The chosen model, as well as the route of drug administration, by comparison, will contribute to the selection of an appropriate equation necessary to characterize the plasma concentration versus time data accurately. The following illustrations and examples, hopefully, will delineate some of the concepts discussed in this section.

**2.1.1 Intravenous bolus administration**

one-compartment model Figure 1.8 is a semilogarithmic (S.L.) plot of plasma concentration versus time data for a drug administered as an intravenous bolus dose. A semilogarithmic plot derives its name from the fact that a single axis (the y-axis in this case) employs logarithmic co-ordinates, while the other axis (the x-axis) employs linear coordinates. The plotted curve is a straight line, which clearly indicates the presence of a single pharmacokinetic phase (namely, the elimination phase.) Since the drug is administered intravenously, there is no absorption phase. The straight line also suggests that distribution is instantaneous; thus, the drug is rapidly distributed in the body. These data can be accurately and adequately described by employing the following mono-exponential equation

(15)

**Cp (µg mL–1)**

**Time (hr)**

Fig 6: A typical plot (semilogarithmic) of plasma concentration (Cp) versus time following the administration of an intravenous bolus dose of a drug that is rapidly distributed in the body.

where Cp is the plasma drug concentration at any time t; and (Cp)o is the plasma drug concentration at time t=0.

Please note that there is a single phase in the concentration versus time plot and one exponential term in the equation required to describe the data. This indicates that a one-compartment model is appropriate in this case.

**2.1.2 Intravenous bolus administration**

two-compartment model Figure 7 clearly shows the existence of two phases in the concentration versus time data. The first phase (curvilinear portion) represents drug distribution in the body; and only after a finite time (indicated by a discontinuous perpendicular line) do we see a straight line. The time at which the concentration versus time plot begins to become a straight line represents the occurrence of distribution equilibrium. This suggests that drug is being distributed slowly and requires a two-compartment model for accurate characterization. The equation employed to characterize this plasma concentration versus time data will be biexponential (contain two exponential terms):

Cp = Ae -αt + Be -βt  (16)

**Distribution or α phase**

**Cp (µg mL–1)**

**Post-distribution or β phase**

**Time (h)**

**Fig 7:** A typical semilogarithmic plot of plasma concentration (Cp) versus time following the administration of an intravenous bolus dose of a drug that is slowly distributed in the body

where A and a are parameters associated with drug distribution and B and b are parameters associated with drug post-distribution phase. Please note that there are two phases in the concentration versus time data in Fig. 7 and that an equation containing two exponential terms is required to describe the data. This indicates that a two-compartment model is appropriate in this case.

**2.1.3 Extravascular administration: one-compartment model**

Extravascular administration can be by a number of routes: · oral administration (tablet, capsule, suspension, etc intramuscular administration (solution and suspension) · subcutaneous administration (solution and suspension) · sublingual or buccal administration (tablet) · rectal administration (suppository and enema) · transdermal drug delivery systems (patch) · inhalation (metered dose inhaler).

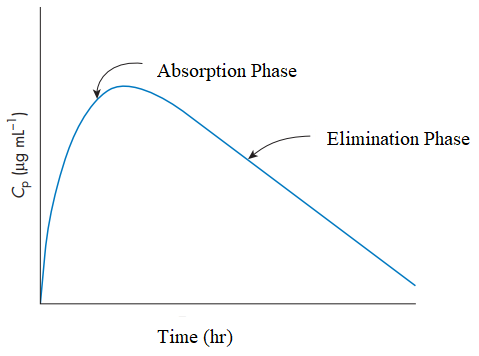


Fig 8: A typical semilogarithmic plot of plasma concentration (Cp) versus time following the extravascular administration of a dose of a drug that is rapidly distributed in t

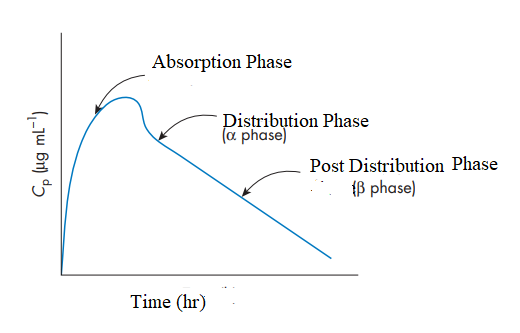
The plasma concentration versus time profile presented in Fig. 8 represents a one-compartment model for a drug administered extravascularly. There are two phases in the profile: absorption and elimination. The onset of action is determined by factors such as formulation and type of dosage form, route of administration, physicochemical properties of drugs and other physiological variables. 3. The entire administered dose of a drug may not always reach the general circulation (i.e., incomplete absorption) However, the profile clearly indicates the presence of only one phase in the post-absorption period. Since distribution is the sole property that determines the chosen compartment model and, since the profile contains only one phase in the post-absorption period, these data can be described accurately and adequately by employing a one-compartment model. However, a biexponential equation would be needed to characterize the concentration versus time data accurately. The following equation can be employed to characterize the data:

(18)

(19)

where Ka is the first-order absorption rate constant, K is the first-order elimination rate constant; (Xa)t=0 is the amount of absorbable drug at the absorption site present at time zero; F is the absorbable fraction; and X0 is the administered dose. Please note that a one-compartment model will provide an accurate description since there is only one post-absorption phase; however, since there are two phases for the plasma concentration versus time data, a biexponential equation is required to describe the data accurately.

**2.1.4 Extravascular route of drug administration, two-compartment model**

****

**Fig 9:** A typical semilogarithmic plot of plasma concentration (Cp) versus time following the extravascular administration of a dose of a drug that is slowly distributed in the body.

Figure 9 clearly shows the presence of three phases in the plasma concentration versus time data for a drug administered by an extravascular route. Three phases include absorption, distribution and post-distribution. Please note that in the figure, there is a clear and recognizable distinction between the distribution and post-distribution phases [9]. Furthermore, the plasma concentration versus time profile, in the post-absorption period looks identical to that for an intravenous bolus two-compartment model (Fig 7). These data, therefore, can be described accurately by employing a two-compartment model and the equation will contain three exponential terms (one for each phase: absorption, distribution, and postdistribution.) It should be stressed that these compartments do not correspond to physiologically defined spaces (e.g. the liver is not a compartment). If the chosen model does not adequately describe the observed data (plasma concentration), another model is proposed. The model that is ultimately chosen should always be the simplest possible model which is still capable of providing an adequate description of the observed data. The kinetic properties of a model should always be understood if the model is used for clinical predictions.

* 1. **Non-Compartmental Models.**

It is also called as Model independent method

• Non–compartmental models describe the pharmacokinetics of drug disposition using time and concentration parameters

• Can be applied to any compartment model provided the drugs or metabolites follow linear kinetics

• This approach based on statistical moments theory, involves the collection of experimental data following a single dose of drug

• If one considers the time course of drug concentration in plasma as a statistical distribution curve, then

(20)

• Mean residence time (MRT) is the average time for the drug molecules to reside in the body • MRT is also known as the mean transit time and mean sojourn time MRT = total residence time for all drug molecules in the body total number of drug molecules MRTiv = 1 KE

• Mean absorption time (MAT) is the difference between MRT and MRTIV after an extravascular route is used

(21)

• Clearance is the volume of plasma cleared of drug per unit time and may be calculated without consideration of the compartment model

* 1. **Physiological Models.**

Physiological Pharmacokinetics models are mathematical models describing

• Drug movement and disposition in the body based on organ blood flow and organ spaces penetrated by the drug

Models are elaborated on the basis of known anatomy and physiology of humans and other animals Incorporates physiological, anatomical and physiochemical data.

MERITS

• Ideally provide an exact description of the time course of drug concentration in any organ or tissue.

•Able to provide greater insight to drug distribution in the body.

• Parameters of these models corresponds to actual physiological and anatomical measures.

• Introduce the possibility of animal scale-up which would provide a rational basis for the correlation of drug data among animal species.

DEMERITS

• Greater requirements for in vitro or in vivo data

• Statistical evaluation of uncertainty and variability more challenging

Model development and implementation requires appropriate expertise

ASSUMPTION

• Exchange of drug between capillary blood and interstitial water is considered to be very rapid.

Cell membrane is considered to be very permeable to the drug.

• Capillary membrane does not offer any resistance to drug permeation.

• Constant ratio of drug concentration between organ and venous blood is quickly established.

TYPES OF MODELS

* Blood flow limited model
* Physiologic Pharmacokinetic Model with Binding
* Membrane limited model

BLOOD FLOW LIMITED MODEL

Drug movement and disposition in the body based on organ blood flow and the organ spaces penetrated by the drug.

In its simplest form, a physiologic pharmacokinetic model considers the drug to be blood flow limited. Drugs are carried to organs by arterial blood and leave organs by venous blood [10].

Differential mass balance equations are written for each compartment to describe the inflow, outflow, accumulation, and disappearance of drug, and are solved simultaneously with the aid of a computer.

Tissue compartment

Blood

Cart, Qt Cven

• Uptake of drug into the tissues is rapid, and a constant ratio of drug concentrations between the organ and the venous blood is quickly established. This ratio is the tissue/blood partition coefficient:

= (22)

where P is the partition coefficient

The magnitude of the partition coefficient can vary depending on the drug and on the type of tissue. for example: Adipose tissue has a high partition for lipophilic drugs.

The rate of blood flow to the tissue is expressed as Q, (mL/min), and the rate of change in the drug concentration with respect to time within a given tissue organ is expressed as

(23)

(24)

where C is the arterial blood drug concentration and C is the venous blood drug concentration. Q, is blood flow and represents the volume of blood flowing through a typical tissue organ per unit of time.

PHYSIOLOGIC PHARMACOKINETIC MODEL WITH BINDING

The physiologic pharmacokinetic model assumes flow- limited drug distribution without drug binding to either plasma or tissues.

In reality, many drugs are bound to a variable extent in either plasma or tissues.

With most physiologic models, drug binding is assumed to be linear (not saturable or concentration dependent). Bound and free drug in both tissue and plasma are in equilibrium. Further, the free drug in the plasma and in the tissue equilibrates rapidly.

1. **Non-linear Pharmacokinetics.**

Nonlinear Pharmacokinetics

• It is also known as capacity-limited, dose-dependent, or saturation pharmacokinetics

• At lower dose, drug shows first order kinetics but at higher dose, it shows zero order due to saturation, so it is also known as Mixed Order Kinetics

• Nonlinear pharmacokinetics do not follow first-order kinetics as the dose increases

• Nonlinear pharmacokinetics may result from the saturation of an enzyme- or carrier-mediated system Characteristics of nonlinear pharmacokinetics

• The AUC is not proportional to the dose

• The amount of drug excreted in the urine is not proportional to the dose

• The elimination half-life may increase at high doses

• The ratio of metabolites formed changes with increased dose Tests to detect non-linearity

• Determine Css (steady state plasma concentration) at different doses and if Css is directly proportional to the doses then it is linear pharmacokinetics else it is nonlinear pharmacokinetics

• Determine some of important pharmacokinetic parameters such as fraction bioavailable F, t1/2, total clearance at different doses. Any change in parameters which are usually constant, means non-linear pharmacokinetics

Causes of non-linearity

1. Drug Absorption

• When the absorption is solubility or dissolution rate limited eg., Griseofulvin

• When absorption involve Carrier mediated transport: saturation at higher dose result in nonlinearity eg., Ribofalvin, Ascorbic acid

• When pre systemic gut wall or hepatic metabolism attains saturation eg., Propranolol

• Changes in gastric blood flow and gastric emptying eg., various diseases, time of administration (Chronopharmacokinetics)

1. Distribution

• Saturation of plasma protein binding e.g., in case of Phenylbutazone

• Saturation of tissue binding sites e.g., in case of Imipramine a. In both the cases, increase in free plasma drug concentration and increase in Vd in the former case where as decrease in Vd in latter case b. Clearance of a drug with high ER is greatly increases due to saturation of binding site

1. Drug Metabolism

• Capacity limited metabolism due to the enzyme or cofactor saturation. Example include Phenytoin, thoephylline, alcohol. Increase Css, decrease CL

• Enzyme induction example in case of carbamazepine where decrease in plasma concentration is observed on repetitive administration over a period of time. Increase CL, decrease Css

• Hepatotoxicity, change in hepatic blood flow and inhibitory effects of metabolites on enzymes

1. Drug Excretion

• Active tubular secretion as in penicillin. Decreases renal clearance

• Active tubular reabsorption as in water soluble vitamins and glucose. Increases renal clearance

• Forced diuresis, change in urine pH, nephrotoxicity Michaelis–Menten kinetics

• It is used to describe nonlinear pharmacokinetics

• The Michaelis–Menten equation describes the rate of change (velocity) of plasma drug concentration:

(25)

Where Vmax is the maximum velocity of the reaction C is the substrate or plasma drug concentration Km is the Michaelis constant equal to the C at 0.5 Vmax

• At low C values, where C << Km, this equation reduces to a first-order rate equation because both Km and Vmax are constants

(26)

• At high C values, where C >> Km, this equation reduces to a zero-order rate equation

(27)

• Show zero-order elimination rates at high drug concentrations, fractional-order elimination rates at intermediate drug concentrations, and first-order elimination rates at low drug concentrations.

1. **Conclusion**

Clinicians will be better able to choose the appropriate medications, dosages, and dosing periods for different individuals if they have an in-depth knowledge of pharmacokinetics and pharmacodynamics. This is very important for professional anaesthetists because it takes numerous drugs to achieve the best anaesthesia. Years of expertise in titrating anaesthetic medications can be viewed as the art in this field, although this subject can be regarded science.

**References**

1. Meyer BH, Welch EH, Milner A, Möhr D. Applied pharmocokinetics. In: Milner A, Welch E, editors. Applied pharmacology in anaesthesiology and critical care. 1st ed. Medpharm Publications (Pty) Ltd; 2012. p. 1-32.

2. Shargel, L., & Yu, A. B. (2015). Applied Biopharmaceutics and pharmacokinetics (7th ed.).

3. Benet, L. Z., & Zia-Amirhosseini, P. (1995). Basic principles of pharmacokinetics. Toxicologic Pathology, 23(2), 115-123. <https://doi.org/10.1177/019262339502300203>

4. Jambhekar, S. S., Breen, P. J., & Royal Pharmaceutical Society of Great Britain. (2012). Basic pharmacokinetics.

5. Dowd, F. J., Johnson, B., & Mariotti, A. (2016). Pharmacology and therapeutics for dentistry - E-book. Elsevier Health Sciences.

6. Daneman, R., & Prat, A. (2015). The blood–brain barrier. Cold Spring Harbor Perspectives in Biology, 7(1), a020412. <https://doi.org/10.1101/cshperspect.a020412>

7. DeGorter, M., Xia, C., Yang, J., & Kim, R. (2012). Drug transporters in drug efficacy and toxicity. Annual Review of Pharmacology and Toxicology, 52(1), 249-273. <https://doi.org/10.1146/annurev-pharmtox-010611-134529>

8. Duckworth, R. M. (2013). Pharmacokinetics in the oral cavity: Fluoride and other active ingredients. Monographs in Oral Science, 125-139. <https://doi.org/10.1159/000350590>

9. Fan, J., & De Lannoy, I. A. (2014). Pharmacokinetics. Biochemical Pharmacology, 87(1), 93-120. <https://doi.org/10.1016/j.bcp.2013.09.007>

10. Gallardo, E., Barroso, M., & Queiroz, J. (2009). Current technologies and considerations for drug bioanalysis in oral fluid. Bioanalysis, 1(3), 637-667. <https://doi.org/10.4155/bio.09.23>

11. Zakeri-Milani, P., & Valizadeh, H. (2014). Intestinal transporters: Enhanced absorption through P-glycoprotein-related drug interactions. Expert Opinion on Drug Metabolism & Toxicology, 10(6), 859-871. <https://doi.org/10.1517/17425255.2014.905543>.