

PHARMACOKINETICS

Abstract

Pharmacokinetics relates to the investigation of drug dynamics within the human body, encompassing the intricate processes of drug absorption, distribution, metabolism, and excretion, commonly referred to as ADME. This chapter presents a brief overview of pharmacokinetics, explaining the way these dynamic processes regulate drug concentration- time patterns and impact therapeutic results. The chapter commences by examining the mechanisms involved in drug absorption, providing a comprehensive understanding of the variables that influence the rate and extent of drug absorption across different routes of administration. The chapter explores the distribution patterns of drugs, emphasizing the impact of blood circulation and protein binding. Subsequently, it also delves into the topic of drug metabolism, elucidating the crucial involvement of enzymes in the process of converting drugs into metabolites. Moreover, this explains the pathways through which drugs are eliminated from the body, with a particular focus on the significance of renal and hepatic clearance in determining the duration of drug activity. The chapter emphasizes the importance of pharmacokinetic parameters, including volume of distribution, and bioavailability, in the prediction of drug behaviour and the optimization of dosing regimens. The insights derived from this chapter will provide valuable assistance to healthcare professionals and researchers in the development of drug regimens that prioritize safety and efficacy. Consequently, this will lead to an improvement in patient care and therapeutic outcomes.

Keywords: Absorption; Distribution; Metabolism; Elimination; Bioavailability

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I. INTRODUCTION TO PHARMACOKINETICS

Pharmacokinetics is a subfield within the discipline of pharmacology that is primarily concerned with elucidating the mechanisms by which the human body metabolizes and eliminates pharmaceutical substances. Pharmacokinetic relates to the investigation into the processes of drug absorption, distribution, metabolism, and excretion, which are commonly denoted as ADME. A comprehensive understanding of pharmacokinetics is imperative to make accurate predictions regarding the behaviour of drugs within the human body, their duration of activity, and the mechanisms by which they are eliminated.

Upon administration, a drug undergoes a series of physiological processes within the human body. Initially, it is essential for the substance to undergo absorption into the circulatory system from its designated point of introduction (e.g., orally, intravenously, or transdermally). Upon entering the circulatory system, the drug undergoes distribution to multiple tissues and organs, including the specific location where it manifests its desired therapeutic effects.

Throughout this procedure, the drug may undergo metabolic transformations, resulting in its conversion into various metabolites. Metabolism is a physiological process that takes place in various tissues, including the liver. Ultimately, the drug or its metabolites are excreted from the organism via urine, faeces, or alternative pathways.

Pharmacokinetics facilitates the comprehension of healthcare practitioners regarding the various factors that impact the processes of drug absorption, distribution, metabolism, and excretion. Understanding this information is crucial to ascertain the correct dosage, frequency of administration, and duration of drug treatment for individuals.

Through the examination of pharmacokinetics, scholars and medical practitioners can make well-informed judgments regarding drug interactions, potential adverse reactions, and optimal methods of drug administration to attain the desired therapeutic effects. Pharmacokinetics holds significant importance in the enhancement of drug therapies and the advancement of patient safety and treatment effectiveness.

II. DRUG ABSORPTION

The word "absorption" is often used to describe how a medicine or medication is absorbed by the body and then subsequently distributed throughout the body. It's a necessary process for the medicine to have its therapeutic effects at the intended site of action. The rate and extent of absorption may vary based on the properties of the medicine and the route of administration (oral, intravenous, or topical). Once the medicine enters the circulation, it may go to wherever it's needed to cure the underlying ailment or alleviate the associated symptoms.

For drug absorption to take place, it is necessary for the drug to pass through biological barriers, such as epithelial or endothelial cells. Only a limited number of drugs exhibit **active transport** across cellular barriers, wherein energy in the form of ATP is required to facilitate the movement of the drug from regions of lower concentration to regions of higher concentration.

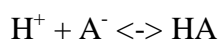
In contrast, most drugs traverse cellular barriers through the process of **passive diffusion**. This mechanism entails the movement of drugs from regions of higher concentration to regions of lower concentration by diffusing across cell membranes. The phenomenon of drug movement described herein is characterized by a lack of energy consumption, yet it is subject to the influence of drug size and solubility.

- 1. Passive Diffusion:** Passive diffusion is widely recognized as the predominant mechanism of drug absorption. The process under consideration can be elucidated by employing the Fick law of diffusion, wherein the drug molecule undergoes movement in accordance with the concentration gradient, moving from regions of higher drug concentration to lower concentration until a state of equilibrium is attained.
- 2. Facilitated Passive Diffusion:** The passive transport of molecules down the concentration gradient is known as facilitated diffusion. It is a selective process, meaning that only certain molecules and ions may flow across the membrane. However, it blocks the passage of other molecules across the membrane. The diffusion of molecules through the membrane is aided by the electric charge and pH.

The lipid-based membrane in living systems establishes compartments that permit the transfer of a certain concentration of water-soluble molecules. The concentration of the ions, small molecules, proteins, and other solutes varies throughout the membranes. Molecules that are hydrophilic, polar, or charged cannot pass the membrane. Examples- Glucose transporter, Ion channels, Aquaporins.

- 3. Active Transport:** Active transport is a process that shows selectivity, requires the expenditure of energy, and potentially involves the transportation of molecules or ions against their concentration gradient. Active transport appears to be restricted to drugs that possess a structural similarity to endogenous substances, such as ions, vitamins, sugars, and amino acids.
- 4. Pinocytosis:** Pinocytosis is a cellular process characterized by the uptake of fluid or particles through their encapsulation by a cell. The cellular membrane undergoes a process of enclosure around the pharmaceutical substance, resulting in the fusion of the membrane to form a fully formed vesicle. Subsequently, this vesicle separates and translocates into the intracellular space.

To optimize drug absorption, it is imperative to consider both the inherent characteristics of the drug and the pH level of the surrounding environment. Most pharmaceutical substances can be classified as either weak acids or weak bases. In the presence of an acidic environment, drugs classified as weak acids have the propensity to acquire a proton, resulting in their deprotonation and subsequent existence in an un-ionized state.

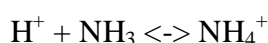


In the illustration, when the weak acid, denoted as A⁻, is introduced into an acidic environment containing H⁺ ions, the pharmaceutical compound acquires a proton, resulting in its deionization (thus transforming into protonated form, HA). When the acid

A⁻ is introduced into an alkaline environment containing -OH, the drug will maintain its ionized state as A⁻.

The ability of drugs to diffuse through a lipid cellular membrane, traverse a biologic barrier, and enter the bloodstream (i.e., be absorbed) is enhanced when they exist in an un-ionized state, instead of being ionized. Therefore, it can be concluded that a drug with weak acidic properties exhibits optimal absorption in acidic surroundings due to its ability to acquire a proton and transition into an un-ionized state.

Contrarily, this statement holds true for drugs classified as weak bases. Let us consider the weak base, NH₃. When exposed to an acidic environment, the drug undergoes protonation, resulting in the acquisition of a proton and subsequent ionization.



Conversely, within an alkaline surrounding, a pharmaceutical compound classified as a weak base would persist in its un-ionized state.

III. DRUG BIOAVAILABILITY

The term "bioavailability" pertains to the degree and pace at which the active component (drug or metabolite) enters the systemic circulation, allowing it to reach the intended site of action.

The bioavailability of a pharmaceutical compound is predominantly influenced by the characteristics of the dosage form, which are influenced in part by its design and manufacturing processes. The clinical significance of variances in bioavailability among different formulations of a specific drug necessitates the understanding of their equivalence.

- **Chemical Equivalence** refers to the presence of the identical active compound in drug products, with the same quantity, conforming to prevailing official standards. Nonetheless, there may be variations in the inactive ingredients among different drug products.
- **Bioequivalence** refers to the state in which drug products, when administered to a single patient using the same dosage regimen, yield comparable levels of the drug in both plasma and tissues.
- **Therapeutic Equivalence** refers to the state in which drug products, when administered to a patient in the same dosage regimen, exhibit identical therapeutic and adverse effects.

IV. FACTORS AFFECTING DRUG ABSORPTION

Certainly! The process of drug absorption can be subject to various factors that have the potential to impact the rate and extent of drug entry into the bloodstream. These factors include:

- 1. Physicochemical Properties of the Drug:** Certain drugs exhibit enhanced absorption due to their specific chemical properties. For example, pharmaceutical substances that exhibit lipid solubility tend to demonstrate enhanced absorption rates compared to substances that possess water solubility. It is possible for drug molecules of smaller size to exhibit enhanced absorption efficiency.
- 2. Route of Administration:** The route of drug administration is a crucial determinant of drug absorption. When drugs are administered intravenously, they are introduced directly into the bloodstream, resulting in rapid and complete absorption. On the other hand, orally administered drugs undergo a process of dissolution, absorption, and metabolism, resulting in potential delays and diminished rates of absorption.
- 3. Drug Formulation:** The way a pharmaceutical product is prepared, such as in the form of tablets, capsules, or solutions, can have an impact on the extent to which the drug becomes absorbed within the human body.
- 4. Gastrointestinal Transit Time:** The duration of drug transit within the gastrointestinal tract can have an influence on the process of absorption. The rate at which a drug traverses the digestive system is influenced by various factors, including gastric emptying rate and intestinal motility.
- 5. Presence of Food and Drug-Food Interactions:** The presence of food in the gastrointestinal tract can have an impact on the absorption of drugs. Certain medications exhibit enhanced absorption when ingested concomitantly with food, whereas others necessitate administration in a fasting state. Certain types of food have the potential to interact with medications, thereby influencing their absorption process.
- 6. pH and Ionization:** The absorption of drugs can be influenced by the pH level of the surrounding environment, especially for drugs that have the potential to undergo ionization and become charged under specific circumstances. As an instance, it is observed that weak acids exhibit enhanced absorption in acidic environments, whereas weak bases demonstrate improved absorption in basic environments.
- 7. Blood Flow to the Absorption Site:** An absorption site that is adequately perfused facilitates the rapid uptake of the drug into the circulatory system. Optimal blood circulation is essential for facilitating the efficient delivery of drugs to their intended target sites.

Comprehending these factors is imperative to optimize drug therapies and guarantee the efficient absorption of medications, resulting in the desired therapeutic effects. Healthcare practitioners consider these factors when prescribing and administering medications to patients.

V. DRUG DISTRIBUTION TO TISSUES

The distribution of drugs to various tissues is a fundamental aspect of pharmacokinetics, a discipline that addresses the movement of drugs within the human body.

Once a drug has been absorbed into the bloodstream, it undergoes systemic distribution through the circulatory system, thereby reaching various tissues and organs within the body. Throughout this physiological progression, the pharmaceutical compound traverses multiple organs, tissues, and cellular structures, thereby eliciting its intended physiological responses.

The process of blood circulation is of paramount importance in the distribution of drugs. The cardiovascular system facilitates the circulation of blood throughout the entire body via arterial pathways. Subsequently, as the blood traverses the intricate network of capillaries, the drug has the potential to diffuse from the bloodstream into the adjacent tissues. The process by which the drug is transported from the bloodstream to the tissues is referred to as capillary perfusion.

The significance of tissue permeability extends to the distribution of drugs as well. To reach their intended target tissues, drugs must traverse multiple cellular barriers. The extent of permeability may exhibit variability across diverse tissues, and certain barriers have the capacity to impede the dispersion of pharmaceutical substances to specific regions within the body. The comprehension of drug distribution to various tissues is imperative in the determination of appropriate dosage and treatment approaches for patients. The consideration of the drug's distribution pattern is a crucial factor for healthcare professionals in determining the optimal dosage and method of administration. This is done to achieve efficient drug delivery to the desired tissues while mitigating any potential adverse effects.

1. Volume of Distribution: The volume of distribution (Vd) is a pharmacokinetic parameter that characterizes the tendency of a specific drug to either stay in the plasma or distribute throughout various tissue compartments. Vd can be defined as a constant of proportionality that establishes a relationship between the overall quantity of a drug present in the body and the drug's concentration in the plasma at a specific moment. The subsequent equation can be utilized to denote Vd:

$$\text{Volume of Distribution (L)} = \frac{\text{Amount of drug in the body (mg)}}{\text{Plasma concentration of drug (mg/L)}}$$

Considering the Equation: A pharmaceutical substance exhibiting a significant amount of distribution (Vd) demonstrates a tendency to exit the plasma and distribute into the extravascular spaces within the body. Consequently, a greater dosage of the drug is necessary to attain a specific concentration within the plasma. A higher volume of distribution (Vd) leads to increased distribution to other tissues.

On the other hand, a pharmaceutical compound that has a low volume of distribution (Vd) exhibits a tendency to persist in the plasma, thereby requiring a lower dosage to attain a desired level of drug concentration in the plasma. A lower volume of distribution (Vd) results in reduced distribution to other tissues. Volume of distribution is highly affected by the acidic-basic nature and lipophilicity of drugs.

2. Plasma Protein Binding: Plasma protein binding is an additional determinant influencing drug distribution. Certain pharmaceutical substances can form complexes with proteins present in the circulatory system, notably albumin. When a drug interacts

with a protein, it undergoes a process of inactivation and establishes a reservoir within the bloodstream. This reservoir plays a crucial role in regulating the quantity of active drug that is available for distribution to various tissues.

Examples: Warfarin, an anticoagulant medication, is frequently administered to prevent the formation of blood clots. The compound exhibits a high affinity for plasma proteins, particularly albumin. Due to its significant affinity for protein binding, a limited proportion of the drug remains unbound and bioactive within the circulatory system. The binding of this protein restricts its dispersion to specific tissues, requiring careful dosage and monitoring to uphold therapeutic efficacy while minimizing the occurrence of adverse effects or bleeding complications.

Aspirin, a commonly utilized analgesic, and anti-inflammatory medication, exhibits a moderate degree of protein binding when present in the circulatory system. Nevertheless, despite its moderate binding affinity, the free concentration of aspirin may exhibit variability among individuals, thereby resulting in variations in its distribution and effectiveness. Various factors, including genetic variations in protein levels, can exert an influence on the distribution and metabolism of aspirin, thereby impacting its anti-inflammatory and analgesic properties.

- 3. Blood-Brain Barrier:** The blood vessels that supply blood to the central nervous system (CNS) exhibit distinctive characteristics known as the blood-brain barrier. This barrier enables these vessels to effectively control the transportation of ions, molecules, and cells between the bloodstream and the brain thereby limiting the distribution of drugs to brain. The effective transportation of pharmaceutical substances to the central nervous system (CNS) continues to pose a significant obstacle in the management of neurological disorders, including Alzheimer's disease, Parkinson's disease, and stroke. The primary obstacle in the delivery of drugs to the central nervous system (CNS) is the existence of the blood-brain barrier (BBB), which restricts the entry of drugs into the brain parenchyma. The blood-brain barrier (BBB) restricts the transportation of drugs by selectively permitting the passage of lipophilic molecules with a low molecular weight (typically less than 400-500 Da) through the transcellular pathway from the bloodstream into the brain. Within this framework, it has been documented that roughly 98% of small molecules and almost all large therapeutic molecules, including monoclonal antibodies, antisense oligonucleotides, and viral vectors, are unable to traverse this barrier.

VI. DRUG METABOLISM

The process of drug metabolism holds significant importance within the field of medical practice and pharmacology. The majority of pharmaceutical substances undergo metabolic transformations within the various physiological systems of the human body, resulting in the formation of metabolites that possess enhanced solubility and are consequently more readily eliminated from the body's tissues. The aforementioned chemical modifications predominantly take place within the liver and are commonly referred to as biotransformation's. Gaining a comprehensive understanding of these changes is essential for effectively implementing the most appropriate pharmacological intervention for every patient, making it a subject of interest for healthcare providers who regularly administer medication to patients.

Biotransformation's are classified into three distinct mechanisms: phase I, phase II, and occasionally phase III. Phase I involves modification, phase II involves conjugation, and phase III encompasses additional modification and excretion.

1. Phase I Modifications involve the chemical alteration of the drug's structure, typically through processes such as oxidation, reduction, hydrolysis, cyclization/decyclization, and the introduction or removal of hydrogen or oxygen. In certain cases, this procedure has the potential to convert a prodrug that is not biologically active into a pharmacologically active drug through metabolic transformations.

Metabolites generated through oxidation processes generally maintain a certain degree of their pharmacological activity. An instance of this phenomenon can be observed in the case of diazepam, a widely used anxiolytic medication, which undergoes phase I modification to produce desmethyldiazepam, followed by further transformation into oxazepam. Both of these metabolites elicit comparable physiological and psychological effects to diazepam itself.

2. Phase II Modifications encompass a series of reactions wherein the drug molecule is conjugated with another molecule, thereby facilitating the coupling process. The process of conjugation typically results in the compound becoming pharmacologically inactive and soluble in water, facilitating its excretion from the body. The mechanisms involved in conjugation encompass various processes, such as methylation, acetylation, sulphation, glucuronidation, as well as glycine or glutathione conjugation. These processes may take place within various organ systems such as the liver, kidney, lungs, intestines, and others.

One instance of phase II metabolism can be observed in the conjugation of oxazepam, the active metabolite of diazepam, with a molecule known as glucuronide. This process turns oxazepam physiologically inactive, allowing for its excretion without undergoing any additional chemical alterations. After the completion of phase II metabolism, there is a subsequent possibility of **phase III**, during which the cellular excretion of conjugates and metabolites takes place.

Enzymatic catalysis of phase I and phase II processes is a crucial determinant in drug metabolism. The precise composition and relative abundance of hepatic enzymes play an essential role in facilitating the effective biotransformation of pharmaceutical compounds. Monoamine oxidase and cytochrome P450 are considered to be the essential enzymes in the field of medicine. These two enzymes play a crucial role in the metabolism of numerous biogenic and xenobiotic compounds. The enzyme monoamine oxidase (MAO) facilitates the enzymatic conversion of monoamines, including serotonin and dopamine. Monoamine oxidase inhibitors (MAOIs) are employed as pharmacological agents for the treatment of depression due to their ability to elevate central nervous system (CNS) levels of serotonin and dopamine. The metabolism of numerous psychoactive drugs, such as amphetamines and opioids, is facilitated by the enzyme cytochrome P450.

VII. DRUG EXCRETION

Drug excretion refers to the process by which drugs are eliminated from the body, either in the form of metabolites or in their original, or unchanged state. Numerous pathways of excretion exist, that includes various bodily fluids such as urine, bile, sweat, saliva, tears, milk, and stool. Undoubtedly, the kidney and liver are the most crucial excretory organs.

- 1. Renal Excretion:** The process of renal excretion plays a vital role in the filtration and elimination of waste products, such as drugs and their metabolites, from the bloodstream by the kidneys. The process described serves as a crucial pathway for the elimination of drugs and their metabolites from the human body, thereby exerting a substantial influence on drug clearance and the maintenance of physiological equilibrium.

Factors Affecting Renal Excretion:

- The excretion process is greatly influenced by the pH level of urine, as it affects the ionization of drugs, which in turn depends on whether the drug is alkaline or acidic. Enhanced elimination is observed when weakly acidic drugs are excreted in alkaline urine, while weakly basic drugs are excreted in acidic urine.
 - GFR is a measurement of the kidneys' ability to filter blood. It determines the rate of substance elimination from the circulation into the urine. A decrease in GFR results in delayed drug excretion and can affect dosing, particularly for medications primarily eliminated by the kidneys.
 - Drugs that exhibit high affinity for plasma proteins, particularly albumin, demonstrate reduced susceptibility to renal filtration and exhibit limited excretion through urine.
 - The renal excretion of a drug can be influenced by its size and lipophilicity. In general, drugs that are smaller in size and possess greater water solubility exhibit enhanced filtration and excretion by the kidneys, in comparison with drugs that are larger in size and possess greater lipid solubility.
- 2. Biliary Excretion:** Certain pharmaceutical substances and their metabolic byproducts are excreted to a significant extent through the biliary system. Active secretory transport is necessary for the transportation of substances across the biliary epithelium, as they are moved against a concentration gradient. When the concentrations of drugs in plasma reach high levels, the process of secretory transport may reach a maximum limit, also known as the transport maximum.

Compounds exhibiting comparable physicochemical characteristics have the potential to engage in competitive interactions during the excretion process. Substances possessing a molecular weight exceeding 300 g/mol, along with the presence of both polar and lipophilic functional groups, exhibit a higher propensity for elimination through the biliary route. Conversely, smaller molecules tend to be excreted in minimal quantities. The process of conjugation, specifically in relation to glucuronic acid, enhances the elimination of substances through the biliary system.

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