PHARMACOKINETICS

Abstract

Pharmacokinetics is the branch of pharmacology that focuses on the study of how drugs move within the body. It include the processes of drug absorption, distribution, metabolism, and elimination, collectively known as ADME. The main objective of pharmacokinetics is to quantitatively describe the time course and extent of drug concentration at different sites within the body, such as blood plasma, tissues, and organs. This knowledge helps in predicting the drug therapeutic effect, as well as potential side effects and interactions with other drugs. The pharmacokinetic parameters commonly studied include absorption rate, distribution volume, clearance, half-life, and bioavailability.

Key words: Pharmacokinetic, Absorption, Distribution, Metabolism, Elimination.

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I. INTRODUCTION

Pharmacokinetics is the branch of pharmacology that focuses on the study of how drugs move within the body. It include the processes of drug absorption, distribution, metabolism, and elimination, collectively known as ADME. Pharmacokinetics plays a crucial role in understanding how drugs are processed by the body, as well as in determining the dosage and frequency of drug administration.

The main objective of pharmacokinetics is to quantitatively describe the time course and extent of drug concentration at different sites within the body, such as blood plasma, tissues, and organs. This knowledge helps in predicting the drug's therapeutic effect, as well as potential side effects and interactions with other drugs.

The pharmacokinetic parameters commonly studied include absorption rate, distribution volume, clearance, half-life, and bioavailability.

Absorption is the process by which a drug enters the bloodstream after administration, which can take place through various routes such as oral ingestion, inhalation, injection, or topical application.

Distribution involves the movement of a drug all over the body via the bloodstream, allowing it to reach its target site(s) of action.

Metabolism, often carried out by enzymes in the liver, transforms drugs into metabolites that can be more easily eliminated from the body. Elimination involves the removal of drugs and their metabolites from the body, mainly through urine and feces. The half-life of a drug is the time it takes for the concentration of a drug in the body to decrease by half, and it is used to estimate the dosing interval required to maintain therapeutic levels.

Pharmacokinetic studies utilize mathematical models and experimental techniques to measure drug concentrations over time, allowing for the estimation of various pharmacokinetic parameters. These studies help optimize drug therapy by determining appropriate dosing regimens, identifying factors that may alter drug absorption or elimination, and assessing the impact of patient characteristics on drug disposition.

Overall, pharmacokinetics provides a systematic framework for understanding how drugs are processed within the body, which is essential for ensuring safe and effective drug use in clinical practice. By studying the ADME processes and their variability, pharmacokinetics contributes to the development of personalized medicine and the optimization of drug therapy for individual patients.

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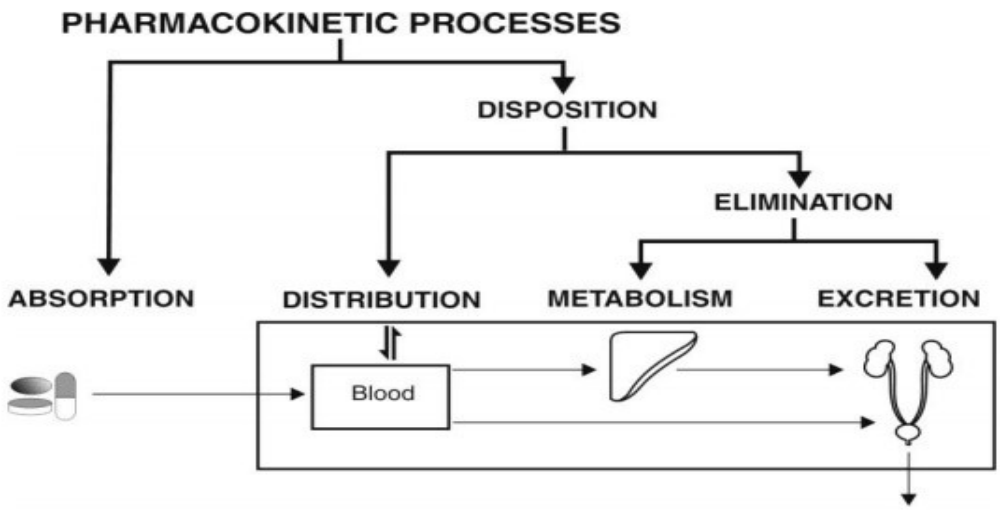

Figure 1: Schematic illustration of pharmacokinetic processes

II. ABSORPTION

Absorption is the process by which a drug enters the bloodstream and becomes available for distribution throughout the body. It is a critical pharmacokinetic parameter that determines the rate and extent to which a drug reaches its target site(s) of action.

The absorption of a drug can take place through various routes of administration, including oral ingestion, inhalation, injection (intravenous, intramuscular, subcutaneous), transdermal (through the skin), and others. The specific route of administration greatly influences the absorption characteristics of a drug.

In the case of oral administration, which is the most common route, the drug is typically ingested in the form of tablets, capsules, or liquids. After ingestion, the drug must pass through the gastrointestinal tract, where it encounters various barriers before reaching the systemic circulation. These barriers include the acidic environment of the stomach, enzymatic degradation in the gastrointestinal fluids, and the intestinal epithelium.

1. Several factors affect the absorption of a drug:

- **Formulation:** The formulation of a drug can significantly influence its absorption. Factors such as the drug's solubility, particle size, and presence of excipients can affect its dissolution and subsequent absorption.

- **Drug properties:** The physicochemical properties of a drug, such as molecular weight, lipophilicity, and ionization state, can impact its ability to cross biological barriers and be absorbed. Lipophilic drugs tend to be better absorbed than hydrophilic drugs.

- **Route of administration:** Different routes of administration have varying absorption characteristics. For example, intravenous administration bypasses the absorption process altogether, resulting in immediate and complete drug availability.

- **Blood flow:** Adequate blood flow to the site of administration is crucial for drug absorption. It ensures an efficient supply of the drug to the systemic circulation.

- **Solubility:** The solubility of a substance in a particular solvent or medium can significantly impact its absorption. Substances that are more soluble in the medium at the absorption site are more likely to be absorbed effectively. For example, hydrophilic (water-soluble) substances tend to be absorbed more readily in aqueous environments, while lipophilic (fat-soluble) substances are better absorbed in lipid-rich environments.

- **Molecular size and shape:** The size and shape of molecules can influence their ability to cross biological membranes. Generally, smaller molecules have an easier time crossing cell membranes compared to larger molecules. Additionally, molecules with a more compact and favorable shape for interaction with transporters or receptors at the absorption site may be absorbed more efficiently.

- **Partition coefficient:** The partition coefficient is a measure of the distribution of components between two immiscible phases, such as oil and water. It indicates the tendency of a substance to preferentially dissolve in one phase over the other. A higher partition coefficient generally indicates better absorption, especially for lipophilic substances, as they can more readily cross lipid membranes

- **PH and enzymatic activity:** The pH of the environment can affect drug ionization, which, in turn, influences its absorption. Enzymatic activity in the gastrointestinal tract can also affect the breakdown and absorption of certain drugs.

- **Drug-drug interactions:** Some drugs can interact with each other, altering the absorption of one or both drugs. For example, certain drugs can inhibit or induce drug-metabolizing enzymes, affecting the absorption of co-administered drugs.

- **Surface area and contact time:** The surface area available for absorption and the duration of contact between the substance and the absorbing surface can affect absorption. Larger surface areas, such as in the case of a highly vascularized organ like the intestines, provide more opportunities for absorption. Prolonged contact time can also increase absorption, as it allows more time for molecules to diffuse or interact with transporters.

Once a drug is absorbed, it enters the bloodstream and is distributed to various tissues and organs throughout the body, where it exerts its therapeutic effect. The rate and extent of absorption, as well as the variability between individuals, play a crucial role in determining the dosage regimen and therapeutic outcomes of a drug. Pharmacokinetic studies help characterize the absorption profile of drugs, enabling healthcare professionals to optimize drug therapy and ensure its efficacy and safety.

III. MECHANISM OF ABSORPTION

Absorption is the process by which substances are taken up or assimilated into another substance. In various fields of science, such as biology, chemistry, and pharmacology, absorption mechanisms can differ based on the nature of the substances involved.

In biological contexts, absorption commonly refers to the uptake of substances across biological membranes. This process is crucial for the absorption of nutrients, drugs, and other molecules in organisms. The mechanism of absorption can vary depending on the nature of the substance and the characteristics of the membrane involved. Here are a few mechanisms of absorption:

Active and passive transport are two fundamental processes involved in the movement of substances across biological membranes. These processes play crucial roles in various physiological functions, including nutrient uptake, waste removal, and cell signaling.

1. **Passive Transport**:Passive transport is the transfer of materials across a membrane without the cell having to exert any energy. It occurs along the gradient of concentration, or the differential in substance concentration between two areas. The following categories can be used to further categorize passive transport:

    - **Simple Diffusion**: In this type of diffusion, chemicals pass right through the membrane's lipid bilayer. Oxygen and carbon dioxide, two small, non-polar molecules, can freely diffuse across the membrane.

    - **Facilitated Diffusion:** In facilitated diffusion, specialized membrane proteins known as transporters or channels aid in the flow of molecules across the membrane. Larger, more polar molecules or ions that are difficult to pass through the lipid bilayer are transported by this method. Along the concentration gradient, assisted diffusion also takes place without requiring energy.

2. **Active Transport:** Active transport is the movement of molecules across a membrane against the gradient of their concentration, from a region of lower concentration to a region of greater concentration. Energy must be used for this process, often in the form of adenosine triphosphate (ATP). Specific membrane proteins known as pumps or transporters are responsible for active transport. Active transportation mostly comes in two forms::

    - **Primary Active Transport**: In primary active transport, ATP is used directly by the transporter protein to push molecules against their concentration gradient across the membrane. The sodium-potassium pump, which keeps the concentration gradients of sodium and potassium ions in animal cells, is an example of primary active transport.

    - **Secondary Active Transport:** In secondary active transport, a drug is transported against its concentration gradient by using the energy stored in the electrochemical gradient of another substance. The energy is produced by the principal active transport-established downward movement of a single material, such as sodium ions.

One illustration is the sodium-glucose co-transporter, which links sodium ion movement downward with glucose transit upward.

3. **Endocytosis and Exocytosis:**These mechanisms involve the formation of vesicles, which are small sacs made of membrane material. Endocytosis is the process by which cells engulf substances by forming vesicles around them, while exocytosis is the reverse process of releasing substances by fusing vesicles with the cell membrane.

IV. DISTRIBUTION

The distribution of a drug is to its movement all over the body after it has been absorbed into the bloodstream. Once a drug enters the bloodstream, it is carried to various tissues and organs where it exerts its pharmacological effects. The distribution of a drug is influenced by several factors, including its physicochemical properties, the characteristics of the body tissues, and the physiological processes involved. Here is a general overview of the drug distribution process:

- **Bloodstream:** After absorption, the drug enters the systemic circulation, where it is carried by the bloodstream throughout the body. The drug may be bound to plasma proteins to varying extents, which can affect its distribution.

- **Capillary Exchange:** Capillaries, the smallest blood vessels, play a vital role in drug distribution. They have thin walls that allow for the exchange of substances between the blood and the surrounding tissues. The drug can diffuse out of the capillaries and enter the interstitial fluid that surrounds the cells.

- **Tissue Perfusion:** The distribution of the drug within different tissues depends on their blood flow rates. Highly perfused tissues, such as the liver, kidneys, heart, and brain, receive a greater blood supply and thus tend to accumulate higher drug concentrations. Less perfused tissues, such as adipose (fat) tissue, may have lower drug concentrations.

- **Binding and Free Drug:** In the bloodstream and tissues, drugs can exist in two forms: bound and free. Some drugs bind to plasma proteins, such as albumin, which can limit their distribution. Only the unbound or free drug is available to exert its pharmacological effects.

- **Blood-Brain Barrier (BBB):** The BBB is a specialized barrier that separates the circulating blood from the brain tissue. It restricts the passage of many drugs and substances, preventing them from freely entering the brain. Only drugs with specific characteristics (e.g., small size, lipophilicity) can cross the BBB and affect the central nervous system.

- **Redistribution and Elimination:** Over time, the drug may undergo redistribution, moving from highly perfused tissues to less perfused tissues or being metabolized and eliminated from the body. Redistribution can affect the duration of drug action.

It's important to note that drug distribution can vary depending on factors such as drug formulation, route of administration, and individual patient factors. Pharmacokinetic studies help determine the distribution characteristics of drugs, including volume of distribution (Vd), which quantifies the apparent space in the body available to contain the drug.

Overall, the distribution of a drug is a complex process influenced by multiple factors, and understanding these factors is essential for optimizing drug therapy and predicting the drug's effects in different tissues and organs.

1. **Factor affecting distribution:**Several factors can influence the distribution of a drug within the body. These factors include:

- **Physicochemical Properties of the Drug:** The physicochemical characteristics of a drug, such as its molecular weight, size, lipophilicity (ability to dissolve in lipids), and ionization status, can affect its distribution. Lipophilic drugs tend to distribute more readily into tissues, including adipose (fat) tissue, while hydrophilic drugs may have limited penetration into certain tissues.

- **Blood Flow to Tissues:** The blood flow to different tissues and organs plays a crucial role in drug distribution. Highly perfused tissues, such as the liver, kidneys, heart, and brain, receive a larger blood supply and therefore tend to accumulate higher drug concentrations. Conversely, tissues with lower blood flow rates, such as adipose tissue, may have lower drug concentration.

- **Plasma Protein Binding:** Many drugs bind to plasma proteins, primarily albumin. Drug molecules that are bound to plasma proteins are less able to distribute into tissues, as only the unbound or free drug can penetrate the tissues and exert its effects. Drug interactions or conditions that alter protein binding can impact drug distribution.

- **Tissue Binding:** Some drugs can bind specifically to tissues or cellular components within tissues. This binding can affect drug distribution by sequestering the drug within certain tissues or limiting its distribution to target sites.

- **Blood-Brain Barrier (BBB):** The BBB is a specialized barrier that separates the circulating blood from the brain tissue. It restricts the entry of many drugs and substances into the brain, preventing them from exerting pharmacological effects. Only drugs with specific characteristics, such as low molecular weight and high lipophilicity, can cross the BBB and affect the central nervous system.

- **Tissue Barriers and Membrane Permeability:** Various tissues possess barriers or specific cellular membranes that can limit the penetration of drugs. For example, the gastrointestinal epithelium, placental barrier, and blood-testis barrier are examples of anatomical barriers that can influence drug distribution.

- **Disease States and Pathophysiological Conditions:** Certain disease states or pathophysiological conditions can alter drug distribution. For example, liver or kidney diseases may impair drug metabolism or excretion, leading to higher drug

concentrations in the body. Additionally, inflammation or infection in specific tissues can affect local drug distribution.

- **Genetic Factors:** Genetic variations in drug-metabolizing enzymes, drug transporters, or drug targets can influence drug distribution. These genetic factors can impact the rate of drug metabolism, the affinity of drug transporters, or the sensitivity of drug targets, ultimately affecting the distribution of drugs within the body.

- Understanding these factors and their impact on drug distribution is crucial for optimizing drug therapy, predicting drug effects in specific tissues, and minimizing potential side effects or toxicities. It highlights the need for individualized dosing regimens based on factors specific to the patient and the drug being administered.

2. **Protein binding:**Protein binding refers to the extent to which a drug binds to proteins in the bloodstream, primarily albumin. When a drug is administered, it can exist in two forms: bound to proteins and unbound or free. The portion of the drug that is bound to proteins is considered inactive, while the unbound fraction is responsible for exerting pharmacological effects.

Protein binding can have significant implications for a drug's distribution, metabolism, elimination, and overall pharmacokinetics. Here are some key points about protein binding of drugs:

- **Albumin Binding:** The majority of drug binding occurs with the plasma protein albumin. Albumin has several binding sites that can interact with drugs, and it is the most abundant protein in the blood. Many drugs, particularly acidic and neutral drugs, exhibit a high affinity for albumin.

- **Other Protein Binding:** In addition to albumin, drugs can also bind to other plasma proteins, such as alpha-1 acid glycoprotein (AAG), lipoproteins, and globulins. The binding affinity and capacity of these proteins vary depending on the drug and the protein involved.

- **Influence on Drug Distribution:** Protein binding can affect the distribution of a drug within the body. Only the unbound or free drug is able to cross biological membranes and reach its target sites. Drugs with high protein binding tend to have limited distribution into tissues compared to drugs with low protein binding.

- **Drug-Drug Interactions:** Protein binding can be affected by other drugs or substances in the bloodstream. W hen two drugs that both bind to proteins are administered together, they may compete for binding sites on the proteins. This can lead to displacement of one drug by another, increasing the concentration of the displaced.

  - drug in its free form, potentially altering its pharmacokinetics and effects.
  - Clinical Implications: Protein binding has implications for drug dosing and pharmacological response. Drugs with high protein binding are more likely to be affected by changes in protein levels, such as in certain disease states (e.g., liver or

kidney disease), malnutrition, or during pregnancy. Altered protein binding can result in higher free drug concentrations, leading to increased drug effects or potential toxicity.

Measurement of Protein Binding: Protein binding is commonly measured using in vitro techniques. The fraction of drug bound to proteins is determined by equilibrium dialysis or ultrafiltration methods. The results are expressed as the percentage of drug bound to proteins.

It is important to consider protein binding when prescribing medications, particularly drugs with a narrow therapeutic index or those known to have significant protein binding. Individual patient factors and potential drug-drug interactions should be taken into account to ensure appropriate dosing and minimize the risk of adverse effects.

V. METABOLISM

Drug metabolism refers to the biochemical processes by which the body modifies drugs to make them more water-soluble and facilitate their elimination from the body. Drug metabolism primarily occurs in the liver, although other organs such as the kidneys, lungs, and intestines can also contribute to the overall process. Here are some key points about drug metabolism:

1. **Phase I Metabolism:** Phase I metabolism involves the introduction or exposure of functional groups on the drug molecule through oxidation, reduction, or hydrolysis reactions. The most common enzyme systems involved in phase I metabolism are the cytochrome P450 (CYP) enzymes. CYP enzymes oxidize drugs by adding oxygen or removing hydrogen, which can increase the polarity and facilitate subsequent elimination. phase 1 metabolism, several common reactions can occur to modify drugs and other foreign compounds. These reactions include:

- **Oxidation**: This is the most common reaction in phase 1 metabolism. Oxidation reactions involve the addition of oxygen or the removal of hydrogen from the compound. They are catalyzed by enzymes known as cytochrome P450 (CYP) enzymes. Examples of oxidation reactions include hydroxylation, N-oxidation, and dealkylation.

- **Reduction**: Reduction reactions involve the addition of electrons to the compound, typically resulting in the reduction of functional groups. This reaction can be catalyzed by various enzymes, including reductases. Reduction reactions are less common than oxidation reactions but still play a significant role in phase 1 metabolism.

- .**Hydrolysis:** Hydrolysis reactions involve the cleavage of chemical bonds through the addition of water. These reactions are catalyzed by enzymes called esterases and amidases. Hydrolysis reactions can lead to the breakdown of esters, amides, and other functional groups.

- **Dealkylation:** Dealkylation reactions involve the removal of alkyl groups from a compound. For example, N-dealkylation involves the removal of an alkyl group from the nitrogen atom in a molecule. Dealkylation reactions can be catalyzed by various CYP enzymes.

- Deamination: Deamination reactions involve the removal of an amino group (-NH2) from a compound. These reactions are catalyzed by enzymes called deaminases. Deamination can convert primary amines to aldehydes or ketones.

- **Hydroxylation:** Hydroxylation reactions involve the addition of a hydroxyl group (-OH) to a compound. This reaction is catalyzed by various CYP enzymes. Hydroxylation can occur at different positions in the molecule, leading to the formation of hydroxylated metabolites.

2. Phase II Metabolism: In phase II metabolism, the medication or its phase I metabolites are coupled with endogenous molecules such glutathione, glucuronic acid, sulfate, or amino acids. These conjugation events make the medication more water-soluble, which speeds up excretion from the body. UDP-glucuronosyltransferases (UGTs), sulfotransferases (SULTs), and glutathione S-transferases (GSTs) are typical phase II enzymes.

In phase 2 metabolism, also known as conjugation or synthetic reactions, drugs and other foreign compounds undergo further modifications through the addition of endogenous molecules. These reactions result in the formation of conjugates that are more water-soluble and easier to eliminate from the body. Some common reactions in phase 2 metabolism include:

- **Glucuronidation:** Glucuronidation is the most prevalent phase 2 reaction. It involves the addition of a glucuronic acid moiety to the compound, catalyzed by UDP glucuronosyltransferase (UGT) enzymes. Glucuronidation can occur at various functional groups, such as hydroxyl (-OH), carboxyl (-COOH), and amine (-NH2), leading to the formation of glucuronide conjugates.

- **Sulfation:** Sulfation involves the addition of a sulfate group (-SO3) to the compound. This reaction is catalyzed by sulfotransferase enzymes. Sulfation commonly occurs with phenols, alcohols, and amines, resulting in the formation of sulfate conjugates.

- **Methylation:** Methylation reactions involve the addition of a methyl group (-CH3) to the compound. Methylation is catalyzed by methyltransferase enzymes, including catechol-O-methyltransferase (COMT) and thiopurine methyltransferase (TPMT). Methylation can occur at various functional groups, such as hydroxyl (-OH) and amine (-NH2), leading to the formation of methylated conjugates.

- **Acetylation:** Acetylation reactions involve the addition of an acetyl group (-COCH3) to the compound. This reaction is catalyzed by acetyltransferase enzymes, such as N-acetyltransferase (NAT). Acetylation commonly occurs with aromatic amines and hydrazines, resulting in the formation of N-acetyl conjugates.

- **Glutathione Conjugation:** Glutathione conjugation, also known as glutathionylation or mercapturic acid formation, involves the addition of glutathione (-GSH) to the compound. This reaction is catalyzed by glutathione S-transferase (GST) enzymes. Glutathione conjugation is particularly important in detoxifying electrophilic compounds, such as reactive metabolites and xenobiotics.

- **Enzyme Induction and Inhibition:** Drug metabolism can be influenced by various factors, including drug-drug interactions. Some drugs can induce or increase the activity of drug-metabolizing enzymes, leading to accelerated metabolism of other drugs. On the other hand, certain drugs or substances can inhibit specific drug-metabolizing enzymes, resulting in decreased drug metabolism and potentially increased drug concentrations and effects.

- **Genetic Variability:** Genetic factors can play a significant role in drug metabolism. Polymorphisms (variations) in drug-metabolizing enzymes can affect an individual's ability to metabolize certain drugs. Genetic variations in CYP enzymes, for example, can result in differences in enzyme activity, leading to variations in drug efficacy and susceptibility to adverse drug reactions.

- **Prodrugs:** Some drugs are administered in an inactive form and require biotransformation by metabolism to become pharmacologically active. These drugs are called prodrugs, and their metabolism is essential for their therapeutic effects.

- **Metabolite Activity:** Drug metabolism can lead to the formation of active metabolites that contribute to the overall pharmacological effects. These active metabolites may have different pharmacokinetic or pharmacodynamic properties compared to the parent drug.

- **Enterohepatic Circulation:** Some drugs and their metabolites can undergo reabsorption from the intestines back into the bloodstream via the bile. This process, known as enterohepatic circulation, can prolong the duration of drug action and contribute to drug accumulation.

- Understanding drug metabolism is crucial for optimizing drug therapy, predicting drug interactions, and minimizing the risk of adverse drug reactions. It helps explain differences in drug response among individuals and guides the development of dosage regimens that consider factors such as drug clearance, half-life, and potential drug-drug interactions.

VI. ELIMINATION

Elimination refers to the process by which drugs and their metabolites are removed from the body. Drug elimination typically occurs through several routes, including renal (via the kidneys), hepatic (via the liver), biliary (via the bile), pulmonary (via the lungs), and other routes like sweat and breast milk. Here are the main mechanisms of drug elimination:

1. **Renal Excretion**: By filtering medicines and their metabolites from the bloodstream and excreting them in urine, the kidneys play a critical role in drug clearance. Renal

elimination involves two main processes: glomerular filtration and tubular secretion. Lipophilic drugs that are not extensively bound to plasma proteins are filtered through the glomerulus into the tubules, where they can undergo reabsorption or active secretion. Hydrophilic or highly ionized drugs are less likely to be reabsorbed and are excreted more readily in the urine.

2. **Hepatic Metabolism and Biliary Excretion:** The liver is responsible for metabolizing many drugs through phase I and phase II metabolism, as mentioned in the previous response. Once metabolized, drugs and their metabolites can be excreted into the bile. Biliary excretion can involve direct secretion into the bile canaliculi or metabolism to more water-soluble forms before excretion. The bile is then released into the intestines, and drugs can be eliminated in feces or undergo enterohepatic circulation.

3. **Pulmonary Excretion:** Some volatile or gaseous drugs can be eliminated through the lungs via exhalation. These drugs are typically small molecules with high vapor pressures, allowing them to be readily eliminated through the respiratory system.

4. **Sweat and Saliva:** Small amounts of drugs can be eliminated through sweat and saliva. However, this route of elimination is generally not significant compared to renal and hepatic excretion.

5. **Other Routes:** Some drugs and their metabolites can be eliminated via other routes, such as breast milk, tears, and exocrine glands.

The rate of drug elimination can be quantified using pharmacokinetic parameters such as clearance and half-life. Clearance represents the ability of the body to eliminate a drug and is typically expressed as volume per unit of time (e.g., milliliters per minute). Half-life refers to the time required for the drug concentration in the body to decrease by half and provides an estimate of the duration of drug action and the time required for elimination.

The term "clearance" in pharmacology refers to the rate at which a drug is eliminated from the body. It is a pharmacokinetic parameter that quantifies the ability of the body to remove the drug from the systemic circulation.

Drug clearance is typically measured in units of volume per unit of time, such as milliliters per minute (mL/min) or liters per hour (L/hr). Clearance can be calculated using various methods, including renal clearance, hepatic clearance, and total body clearance.

Renal clearance refers to the elimination of drugs primarily through the kidneys via urine. It depends on factors such as glomerular filtration, tubular secretion, and tubular reabsorption.

Hepatic clearance refers to the elimination of drugs by the liver through processes like metabolism and biliary excretion.

Total body clearance represents the overall elimination of a drug from the body, taking into account both renal and hepatic clearance.

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