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A Comprehensive Review of Toxicokinetics

Souram Sravanthi[1], Syeda Nishat Fathima[2]
[1,2]Department of Pharmacy Practice, Jayamukhi College of Pharmacy,
Narsampet, Warangal (R), Telangana
Corresponding Author: Souram Sravanthi
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Abstract:
Toxicokinetics is the description of both what rate a chemical will enter the body and what occurs to excrete and metabolize the compound once it is in the body. Toxicokinetics refers to the study of absorption, distribution, metabolism/ biotransformation, and excretion (ADME) of toxicants/xenobiotics in relation to time. Toxicokinetics represents the extension of kinetic principles to the study of toxicology and encompasses applications ranging from the study of adverse drug effects to investigations on how disposition kinetics of exogenous chemicals derived from either natural or environmental sources (generally referred to as xenobiotics) govern their deleterious effects on organisms, including humans. This review provides a comprehensive overview of toxicokinetics, highlighting the essential principles of toxicokinetics in toxicology and risk assessment, as well as its applications in various fields.

Keywords: Toxicology; Toxicokinetics; Principles

Introduction:

Toxicokinetics describe the absorption, distribution, metabolism, and excretion, with time, of foreign compounds in the body. By establishing the relationship between dose-exposure and exposure-toxicity, Tokicokinetics allows for the assessment of toxicity effects, mechanisms in target organs and tissues, and the associated risks to human health. [1]

Absorption:

Absorption is the major process by which toxicants are transported across body membranes. The main sites of absorption of toxic agents are the skin, lungs, and gastrointestinal tract. Many toxicants can be absorbed through the skin and enter the bloodstream. Chemical or physical injury and other circumstances can increase the skin's permeability. Toxicants that are absorbed by the lung are in the form of gases or solid or liquid aerosols. Absorption can be rapid and complete because the lungs have a large surface area and a blood supply that is close to inhaled air in the alveolae. A variety of environmental toxicants enter the food chain and are absorbed from the gastrointestinal tract. Many factors alter the gastrointestinal absorption of toxicants, including gastrointestinal motility, the physical and chemical properties of the toxicant, and gastrointestinal content.

Distribution:

Once a toxicant enters the bloodstream, it is available for distribution throughout the body. Only free toxicants—those not bound to plasma proteins—are able to enter other sites. Such binding is of particular concern to toxicologists and medical scientists, because toxicants bound to those proteins can be displaced by other chemical agents and, once released, go to target organs and produce injury there. The distribution of toxicants depends on their ability to cross cell membranes and on their affinity for various body components. Toxicants vary widely in these two characteristics. Some do not readily cross cell membranes and therefore have restricted distribution. Others bind to various sites in the body, such as fat, liver, kidneys, or bone. The major toxic action of a toxicant might take place where it binds, but often it does not. In fact, binding sites often serve as storage depots whose existence helps to protect the body from the toxic action.

Metabolism and Elimination:

Some chemical agents that enter the body can remain as intact molecules, but many are biologically transformed by metabolic processes. Metabolic processes might involve simple and reversible chemical or physical interactions that primarily affect transport throughout the body and across membranes. In other cases, metabolic processes can substantially alter the chemical nature of the toxicant and create a more toxic or less toxic agent. The metabolic processes can facilitate elimination from the body. It has been useful to consider the metabolic processes as being of two types. The first includes processes of oxidation, reduction, or hydrolysis that primarily alter or add functional (reactive) moieties to the molecule in question. The second includes chemical reactions of pre-existing or newly formed functional groups on the molecule with various endogenous chemicals (such as amino acids, sulfate, and glucuronic acid) to form conjugates, or new chemicals. The

biosynthesis of these products often alters lipid or water solubility and ionization characteristics in ways that promote their secretion and excretion. The major routes for elimination of chemical agents from the body are from the kidneys to urine, from the liver to bile to feces, and from the lungs to exhaled air. Minor routes include secretions from the body—such as sweat, tears, saliva, mucus, digestive juices, and milk—and hair, nails, and desquamated epithelial tissue. As mentioned above, such factors as age and disease state that interfere with kidney function or biliary excretion in the liver can affect the toxic potential of chemicals in the body. The kidney's excretory mechanisms include filtration in the glomeruli and secretion and reabsorption in the renal tubules. Elimination via the kidneys is thus a function of blood flow to the kidneys, molecular volume relative to pore size of the glomerular filter, physicochemical characteristics of the molecule that affect membrane transport, and enzymatic or other systems that might activate or facilitate secretion and reabsorption. Chemicals that bind to large molecules, such as plasma proteins, might not be eliminated by filtration and might be retained in the body for long periods. The liver is especially important as a route of elimination of chemicals that are ingested, because most of the blood from the gastrointestinal tract goes through the liver on its way to the general circulation. The liver is in a unique position to metabolize a chemical through its enzymatic systems and to secrete the metabolites into the bile. Bile empties into the intestines, where the chemical can either be further altered and reabsorbed or be eliminated in the feces. Injury to the liver often affects biliary function and impairs this route of elimination. Elimination of chemicals from the body can be studied by pharmacokinetic measurements, which are often based on the remaining concentration of a chemical or its metabolites in the blood in relation to time. Such information usually provides a good estimate of the amount of the chemical available for toxic action. However, storage of the chemical in tissue depots or the toxicity of unmeasured, activated, intermediate chemical forms is sometimes more important. [2]

Essentials of Toxicokinetics Principles: [3]

The knowledge of kinetic principles is essential in therapeutics because it shows the relationship between the pharmacological or toxicological effects of a drug/ toxicant and the concentration of the drug/toxicant in the body. These principles are useful for determining the following factors:

1. the extent and rate to which pharmacokinetic parameters (ADME) occur in body;
2. the dose and dosing schedule of the drug and their modification according to individual needs;
3. the drug concentrations that produce therapeutic and toxic effects;
4. the drug concentration in various body fluids and tissues, and accumulation of the drug or its metabolites in the body;
5. the half-life (T1/2) and duration of action of the drug;
6. the effect of the disease state on various pharmacokinetic parameters;
7. in the case of animals, the withdrawal time for meats, eggs, and dairy products when the drug is administered to food-producing animals;
8. the nature and extent of drug interactions.

Applications of Toxicokinetics: [4]

- Pharmacokinetic Optimization: Toxicokinetic studies optimizes drug compositions and dosing regimens for therapeutic efficacy and minimal toxicity. Comprehending the processes of drug absorption, distribution, and metabolism facilitates the development of formulations that exhibit enhanced bioavailability and precise delivery to particular tissues.
- Safety Assessment: Toxicokinetic data can reveal probable drug-induced toxicity. Toxicokinetic studies aid in identifying toxicokinetic factors related with adverse outcomes by evaluating the frequency and extent of drug absorption, distribution, and metabolism. This information assists in the evaluation of safety margins and risk evaluations during drug development.
- Drug-Drug Interactions: Toxicokinetic studies have significance for predicting and evaluating interactions between drugs. Drugs may interact with other drugs at different phases of ADME, affecting their pharmacokinetic profiles and potentially resulting in adverse effects or therapeutic failure. Understanding toxicokinetic interactions assists to maximise the effectiveness of drugs combinations while reducing the possibility of unanticipated interactions.
- Individualized Therapy: Toxicokinetic variability in patients influences pharmacological responsiveness and vulnerability to toxicity. Pharmacogenomic research combined with toxicokinetic testing deliver customized medication approaches, allowing for personalized dose regimens based on individual genetic makeup, metabolic capability, and other patient-specific traits.
- Pediatric and Geriatric Populations: Toxicokinetic studies are critical for optimizing medication therapy in vulnerable populations, such as pediatric and geriatric patients. Age-related changes in physiology, metabolism, and organ function affect medication pharmacokinetics and toxicity. Toxicokinetic data are useful for altering dose regimens and

reducing the probability of adverse effects in these populations.

- Regulatory Compliance: Toxicokinetic studies are integral to regulatory submissions for drug approval and marketing authorization. Comprehensive toxicokinetic assessments provide crucial data to regulatory agencies for evaluating drug safety, establishing appropriate dosing guidelines, and determining risk-benefit profiles. Compliance with regulatory requirements ensures the safe and effective use of drugs in clinical practice.
- Post-Marketing Surveillance: Toxicokinetic monitoring continues after drug approval to assess real-world safety and efficacy. Pharmacovigilance programs utilize toxicokinetic data to detect and evaluate adverse drug reactions, monitor long-term effects, and refine risk management strategies. Timely identification of safety concerns improves patient outcomes and informs regulatory decisions regarding drug safety.

Factors Influencing Toxicokinetics of Drugs: [5]

Understanding these factors is paramount for predicting and mitigating the toxic effects of drugs. Some of these factors are:

Physicochemical Properties of Drugs:

- Size of molecules: The size of a toxin molecule can determine its ability to pass through the capillary walls. Generally, smaller molecules can pass through the capillary walls more easily than larger ones. The capillaries in different organs have varying pore sizes, which can also affect the absorption of toxins. For instance, the pores in the glomerular capillaries of the kidneys are large enough to allow the passage of small molecules, while the pores in the capillaries of the blood-brain barrier are much smaller and more selective.
- Molecular Weight: Larger molecules present in toxin/drug may have difficulty crossing biological membranes, affecting their absorption and distribution.
- Lipophilicity: Lipophilic drugs tend to distribute more readily into fatty tissues and across cell membranes, influencing their distribution and metabolism.
- Degree of Ionization: Ionized drugs exhibit altered solubility and permeability characteristics, impacting their absorption and distribution.
- Protein Binding: Drugs/Toxins bound to plasma proteins have reduced distribution and are less readily eliminated, affecting their overall toxicokinetics.
- Porosity of endothelial capillaries: The porosity of capillaries refers to the number and size of pores present in the capillary walls. A higher porosity indicates a larger surface area for exchange and a faster rate of absorption. The capillaries in different organs have varying porosities, which influence the absorption of toxins. For example, the liver has a high porosity, which enables it to rapidly absorb and metabolize toxins.

Route of Administration:

- The method by which a drug is administered (e.g., oral, intravenous, dermal) affects its bioavailability, distribution, and metabolism.
- Different routes of administration result in variations in absorption rates, bioavailability, and onset of action.

Metabolism:

- Drug metabolism primarily occurs in the liver, where enzymes convert drugs into metabolites that are more readily excreted.
- Enzyme activity can be influenced by genetic factors, drug interactions, age, gender, and disease states, leading to variations in drug metabolism among individuals.
- Genetic polymorphisms in drug-metabolizing enzymes (e.g., cytochrome P450 enzymes) can result in poor or rapid metabolism of certain drugs, affecting their toxicokinetics and potentially leading to adverse effects.

Genetic Factors:

- Genetic variations in drug-metabolizing enzymes, transporters, and receptors can lead to interindividual variability in drug response and toxicity.
- Pharmacogenomics studies aim to identify genetic factors that influence drug metabolism and response, allowing for personalized medicine approaches.

Drug-Drug Interactions:

- Concurrent administration of multiple drugs can lead to interactions affecting drug metabolism, distribution, and excretion.
- These interactions may potentiate or inhibit the effects of drugs, altering their toxicokinetics and increasing the risk of adverse effects.

Age and Gender:

- Pediatric and geriatric populations may metabolize drugs differently due to differences in enzyme activity, organ function, and body composition.
- Gender differences in pharmacokinetics may arise from variations in body fat percentage, hormone levels, and enzyme activities.

Disease States:

- Underlying medical conditions, such as liver or kidney disease, can alter drug metabolism and excretion, affecting toxicokinetics.
- Organ dysfunction may lead to impaired drug clearance and increased susceptibility to drug toxicity.

Nutritional Status:

- Nutritional deficiencies or excesses can influence drug metabolism and distribution, affecting toxicokinetics.
- Certain nutrients may interact with drugs, altering their absorption, metabolism, or excretion.

Environmental Factors:

- Exposure to environmental toxins or pollutants can interact with drugs, affecting their toxicokinetics and increasing toxicity.
- Environmental factors may alter enzyme activity, drug metabolism, and drug interactions.

Conclusion:

Understanding the toxicokinetics of drugs is essential for optimizing drug therapy, minimizing the risk of adverse effects, and ensuring patient safety. Pharmacokinetic studies, toxicological assessments, and advanced modeling techniques play crucial roles in elucidating the complex interactions between drugs and biological systems, thereby facilitating the development of safer and more effective therapeutic interventions.

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