

PEARLS OF LABORATORY MEDICINE

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TITLE: Pharmacokinetics

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Slide 1: Title slide

Hello, my name is <Kamisha Johnson-Davis>. I am an <Associate Professor in the Department of Pathology at the University of Utah and Medical Director of Toxicology at ARUP Laboratories >. Welcome to this Pearl of Laboratory Medicine on “Pharmacokinetics.”

Slide 2: Learning objectives

- The learning objectives are to:
- Discuss the applications of pharmacokinetics and factors that affect drug therapy
- Define pharmacokinetic parameters such as
 - volume of distribution (V_d)
 - half-life ($t_{1/2}$)
 - clearance (CL)
 - area under the curve (AUC)
- Describe the kinetic models for drug elimination

Slide 3: Applications of pharmacokinetics

Pharmacokinetics uses mathematical equations to describe what the body does to the drug or toxin in terms of absorption, distribution, metabolism and elimination. Clinically, we can apply pharmacokinetics to study the relationships between drug dose, drug concentrations and the resulting effects over time.

It is employed in therapeutic drug monitoring to help guide and optimize therapy to determine the dose, determine the frequency of administration to achieve a desired effect and to minimize toxicity, it can also be used to identify drug-drug interactions and troubleshoot failure to respond to therapy. Pharmacokinetics can also help improve patient care in overdose/toxicity cases by estimating the amount of drug or toxin in the body and to evaluate the clearance of the drug or toxic to direct decontamination efforts of compounds that are involved in adverse drug reactions.

Slide 4: Factors that affect drug therapy

Pharmacokinetics can vary from person to person and it is affected by age, gender, diet, environment, body weight and pregnancy, patient's pathophysiology, genetics and drug-drug or food-drug interactions. Drug therapy is impacted by factors that affect pharmacokinetics and pharmacodynamics. Sex differences in body composition, such as total body water, percent body fat, muscle mass, organ size, blood volume and flow and metabolism enzymes will contribute to the interpersonal variability in pharmacokinetics and ultimately the therapeutic effects of the drug. Drug metabolism may be impacted by genetics. Genetic variations may affect how drugs are metabolized in the body. I do not have time to discuss pharmacogenetics; however, this topic will be covered in another presentation.

Drug metabolism and elimination are also influenced by age. For example, children may not have well-developed liver function to extensively metabolize drug, like adults. For some drugs, elimination may occur faster in children, however in elderly patients with compromised kidney, liver or heart function, drug elimination is decreased. Disease, infection and inflammation can decrease drug metabolism, which may prolong the half-life of the drug and duration of drug action. Drug-drug or food-drug and drug-herb interactions could increase or decrease drug metabolism and impact the duration and efficacy of drug action.

Slide 5: Pharmacotherapy

Patient adherence to medication is THE most important component of drug therapy. In order to perform therapeutic drug monitoring (TDM) the patient must take the medication. The drug will undergo liberation, absorption, distribution in the body, metabolism and excretion, which will have an impact on drug concentrations in blood. Pharmacogenetics may ultimately impact drug concentrations in blood and the clinical effect.

Slide 6: Pharmacotherapy

Pharmacodynamics encompasses the processes of interaction of pharmacologically active substances with target sites, and the biochemical and physiologic consequences leading to therapeutic or adverse effects.

Slide 7: Liberation

Drugs that are administered orally, could be taken in a solid form, either as a tablet, capsule, or suspension and must have some solubility within the body fluids, in order to be absorbed in the body and become pharmacologically active. Drug solubility is dependent on the drug formulation, for example, sustained-released forms of drugs are designed to slow the rate of liberation so absorption can take place over a much longer period of time. The dose and frequency of administration can influence the solubility of the drug, for example, in an overdose situation, the drug may not be dissolved in the stomach. Liberation is dependent on the chemistry of drug - whether it is water soluble or lipid soluble, the stability of the drug in acidic pH, and the route of administration based on surface area and permeability.

Slide 8: Factors that affect drug absorption

The rate and extent of drug absorption is dependent on the chemical nature of the drug itself, such as its polarity, pKa, drug formulation and protein binding. The drugs absorbed in body fluids or skin, will diffuse through biological membrane barriers into the bloodstream. Diffusion can occur passively across the concentration gradient, which

is the primary transport mechanism, or active transport, which requires energy, such as ATP; for drug transport across the blood brain barrier, neuronal membranes, renal tubular cells, and hepatocytes. It is important to note that only free, unionized drugs can cross cell membranes. There are several conditions that may influence the extent or rate of drug absorption, which include abnormal gastrointestinal motility, diseases of the stomach and well as of the small and large intestine, gastrointestinal infections, radiation, and interaction with other substances in the gastrointestinal tract, such as food.

Slide 9: Volume of Distribution

Another term in pharmacokinetics is volume of distribution (V_d), which relates to the amount of drug in the body to the concentration of drug in the blood.

Volume of distribution is a theoretical volume into which the total amount of drug administered is distributed at the same concentration found in serum or plasma.

Drug distribution is dependent on the drug and body compartment.

Polar drugs are soluble in water and distribute to blood circulation and are primarily eliminated by the kidneys. Nonpolar drugs are lipid soluble. These drugs typically distribute to the central nervous system, tissue and fat. The drugs are primarily eliminated in feces and bile

Drug distribution to the various body compartments is dependent on blood perfusion.

It will take minutes for drugs to distribute to plasma and well-perfused organs such as the heart, liver, kidney and brain.

It will take minutes to hours for drugs to distribute to muscles and skin.

It will take hours to days for drugs to distribute to fat stores.

Drug can also be distributed to different reservoirs in the body. Many drugs may accumulate in tissues at higher concentrations than those in the extracellular fluids and blood. Fat cells can serve as a stable reservoir for lipid soluble drugs. Therefore, tissue or fat reservoirs can prolong the drug action in the same tissue or at a distant site reached through circulation.

The limitations of V_d is that it may be based on total body water (~ 0.65 L/kg) and it doesn't estimate actual sites of distribution. In addition, volume of distribution may not account for individual differences in protein binding or tissue binding and it requires drug distribution to be complete.

Slide 10: Bioavailability

Now that we have discussed how the drug is absorbed into circulation, we can introduce another key concept: bioavailability. Bioavailability is the percentage of a drug from the original drug product that enters the circulation in an unchanged - non-metabolized - form.

Drugs can be manufactured as a salt, crystal suspension, liposomes, liquid, oil, tablet, gel, capsule or formulated for sustained or extended release. Factors influencing bioavailability include: route of drug administration, drug formulation, stability of the drug in the GI tract, characteristics of the drug for absorption and biotransformation, patient physiology and pathology, such as GI pH, GI motility, blood perfusion, bacterial flora, malabsorption states, kidney, liver and cardiac function and genetics.

Drugs that are administered orally, will undergo first-pass metabolism by the liver and lead to a decrease in drug bioavailability. Drugs administered intravenously or parenterally will bypass first-pass metabolism in the liver and have 100% bioavailability in systemic circulation.

Of note, intermuscular injection of a drug does not guarantee a high percent of drug bioavailability because absorption of the drug is influenced by blood perfusion at the muscular site for injection.

Slide 11: Protein binding

Drug bioavailability is also impacted by serum protein binding of drugs to protein carriers. The binding of drugs to protein carriers, such as albumin and alpha-1-acid glycoprotein affects the distribution drug to the tissues. The amount of drug available for transport across a membrane depends on the concentration of free, non-bound, drug. Some clinically important aspects of serum protein binding of drugs are:

- Drugs that are highly protein-bound may be competitively displaced by another highly protein-bound drug. The pharmacologic effect of the displaced drug will increase as will renal clearance. In disease states characterized by hypoalbuminemia, the concentration of free drug will be higher in disease states characterized by the increase in acute phase proteins (A1AG), the free drug concentration will decrease. Therefore, the pharmacological activity of the drug is proportional to the free (unbound) concentration in blood. Endogenous substances (bilirubin, fatty acids) may displace a highly bound drug and in some patients with renal disease, without hypoalbuminemia, binding may decrease due to changes in protein charges of albumin.

Slide 12: Drug Metabolism

The purpose of drug metabolism is to convert drugs into more hydrophilic metabolites to enhance elimination from the body. The consequences of drug metabolism could lead to the termination of pharmacological activity of the drug, activated pharmacological activity for prodrugs, such as codeine metabolism to morphine, and decreased bioavailability of the drug. The biotransformation of drugs may produce metabolites that are pharmacologically active. In such instances the metabolite should also be measured because it is contributing to the effect of the drug on the patient.

Slide 13: Drug Metabolism

The drug molecules can be metabolized by phase I reactions, which alter chemical structure by oxidation, reduction, or hydrolysis to convert it into a more polar molecule

for elimination. The cytochrome P-450 enzyme system plays an important role in metabolism. This slide also lists other enzymes involved in metabolism.

Slide 14: Drug Metabolism

Drugs can also be metabolized by enzymes for phase II reactions to conjugate with glutathione, glucuronide, sulfate, methyl-groups and acetyl-groups for conversion into water-soluble forms. Several enzymes that are involved in conjugation reactions are listed below.

Slide 15: Drug Excretion/Elimination

Most drug metabolism takes place in hepatocytes, however, metabolism can also occur in GI tract, lung, nasal mucosa and skin. The role of pharmacokinetics is important for drugs with variability in the rate of metabolism in different patients of the general population, who may have a single nucleotide mutation in the gene for the drug metabolism enzymes. Personalized medicine will take into consideration the patient's genetics to help with the selection of the drug and dosing regimen for treatment.

Excretion of drugs or chemicals from the body can occur through the lungs, intestines, kidney and bile. However, renal excretion is a major pathway for the elimination of most water-soluble drugs or metabolites. Changes in renal function may have a profound effect on the clearance and apparent half-life of the parent compound or its active metabolite(s). For example, decreased renal function will cause serum drug concentrations to increase over time while the drug is being administered, which may lead to an increase in the pharmacological effects of the drug.

Slide 16: Kinetic models

Metabolism kinetics can occur at first-order, zero-order or nonlinear kinetics.

First-order kinetics occurs when the amount of drug eliminated is dependent on the concentration of the compound and follows a logarithmic relationship over time. The clearance and V_d does not change with dose or concentration.

Zero-order kinetics occurs when the rate of elimination is NOT dependent on the drug concentration. Examples of drugs that follow zero-order kinetics at high concentrations are: ethanol, phenytoin, salicylates.

Capacity-limited or nonlinear kinetics occurs when the rate of elimination shifts from first-order to zero-order, based on saturation of elimination processes. Essentially any drug can become capacity-limited in an overdose situation.

Slide 17: Clearance (CL) and Elimination half-life ($t_{1/2}$)

Clearance describes the elimination of a drug from blood and the body. It is expressed as a concentration of drug in a volume of blood per unit of time. At steady state concentration, the rate of drug administration is equal to the rate of drug elimination.

The elimination half-life is usually defined as the time required for the amount of drug in blood to decrease to half of the measured concentration. On average, it takes 5 -7 half-lives to eliminate drug from the body.

In the formulas below for half-life, K_e is the elimination rate constant; which is calculated from clearance and volume of distribution.

The elimination half-life is calculated by dividing the natural log of 2 by the elimination rate constant. Factors that affect clearance are: body weight, body surface area, cardiac output, drug-drug interactions, genetics, liver and kidney function, and plasma protein binding.

Slide 18: Pharmacokinetic modeling: one-compartment model

There are two models that are often used to depict the way drugs are handled by the body. The one compartment model shown here is a simple model in which the drug is hypothesized to distribute quickly to the circulation and is uniformly distributed throughout the body as if the entire body was a single compartment.

Slide 19: Pharmacokinetic modeling: two-compartment model

In a two-compartment model, the body is divided into a central compartment which consists of blood and well perfused organs, such as the liver and kidney and the peripheral compartment, which consists of poorly perfused tissues, such as muscle and fat, where the distribution of the drug is slower.

Slide 20: Area under the concentration curve

The Area under the plasma concentration time curve, also known as AUC is used to assess total blood exposure over a period of time, after the drug is administered. Information from the AUC can be used to determine the drug dose and clearance. The area under the curve demonstrates the time for drugs to be absorbed in the blood stream, the maximum concentration in blood at its peak and the lowest drug concentration in blood over time. The AUC is directly proportional to the dose when the drug follows linear kinetics. The AUC is inversely proportional to the clearance of the drug. AUC is a function drug concentration and time so it gives a measure of how long a drug stays in a body. Some drugs are dosed using AUC to measure the maximum tolerated exposure (AUC Dosing). The AUC values can be used to determine other pharmacokinetic parameters, such as clearance or bioavailability.

This slide demonstrates how the AUC can be impacted by clearance. The red dotted line is an example of a patient with normal drug clearance. The blue line with diamonds demonstrates a patient with decreased clearance and higher drug exposure over time, which could lead to toxicity. The black line with triangles is an example of a patient with increased drug clearance and there is decreased drug exposure over time, which may limit drug efficacy.

Slide 21: Summary

- In summary, pharmacokinetics is a key tool for therapeutic drug monitoring to optimize drug dose and dosing intervals, identify of drug-drug interactions and minimize the risk of drug toxicity.
- Thank you for joining me on this Pearl of Laboratory Medicine on “**Pharmacokinetics.**”

Slide 22: References

Slide 23: Disclosures

Slide 24: Thank You from www.TraineeCouncil.org

