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TITLE: Therapeutic Drug Monitoring

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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** >. Welcome to this Pearl of Laboratory Medicine on "**Therapeutic Drug Monitoring**."

Slide 2: Learning objectives

- The learning objectives are to:
- Discuss the rationale for therapeutic drug monitoring, which I will refer to as (TDM)
- Describe how drug therapy is impacted by pharmacokinetics, pharmacodynamics and pharmacogenetics
- I will List various classes of drugs that require TDM
- And Discuss analytical methods available for TDM

Slide 3: What Is TDM?

Laboratories are a significant part of the health care system and for therapeutic drug monitoring, it is important that laboratories work with the healthcare team, including clinicians, pharmacists, nursing staff, and phlebotomy.

TDM is used to personalize drug therapy to enhance the efficacy of the drug and to reduce the risk of toxicity. TDM is reserved for drugs with a well-established

relationship between blood concentration and clinical effect. It is also targeted for drugs with unpredictable pharmacokinetic-pharmacodynamic relationships with dose as well as drugs with a narrow therapeutic index.

Slide 4: Therapeutic Index

The therapeutic index is the ratio between the toxic dose in 50% of subjects and the therapeutic dose of a drug that is effective in 50% of patients. The therapeutic index is used as a measure of the relative safety of the drug for a particular treatment. For many drugs, there are severe toxicities that occur at sub-lethal doses in humans, and these toxicities often limit the maximum dose of a drug. Drugs with a higher therapeutic index are preferable to a narrow index. Drugs with narrow index require close drug monitoring.

Slide 5: Indications for TDM

TDM is also indicated to assess the detection of non-adherence to drug therapy, which represents a frequent and important cause of preventable adverse reactions. Drug monitoring is employed to ensure that the patient's drug concentrations are within the therapeutic range. It is utilized to assess the cause of toxicity or adverse drug reactions. Clinical signs and symptoms of toxicity are often an effective way to detect treatment failure. Therapeutic drug monitoring can be used to evaluate the clinical presentation of the patient and to monitor decontamination efforts for patients with toxicity.

Slide 6: Recommended drug classes for TDM

The recommended drug classes for therapeutic drug monitoring include: Antiarrhythmics, Antibiotics, Anti-cancer drugs, Antidepressants, Antiepileptics Antipsychotics, Bronchodilators, Cardiac drugs, HIV drugs, Immunosuppressant drugs and Lithium

It is important to note that TDM services should be based on the needs of clinicians and clinical studies from the literature.

Slide 7: Drug Therapy is Impacted by Pharmacokinetics and Pharmacodynamics

Patient adherence to medication is an important component of TDM. In order to perform TDM the patient must take the medication. The drug is liberated, absorbed, distributed in the body, metabolized and excreted, which will have an impact on drug concentrations in blood. The concentration of drug at the site of action can lead to a clinical effect. Physicians can also assess patient adherence to medications from TDM.

Pharmacokinetics describes the processes of the uptake of drugs by the body, the distribution of the drugs into tissue, metabolism and the elimination of the drugs and their metabolites from the body.

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.

Pharmacogenetics describes how genetics can impact drug metabolism and the clinical effect of the drug.

Slide 8: Drug absorption

Drugs that are taken orally are absorbed in the lumen of the small intestine are carried by the portal vein directly to the liver. The liver may extensively metabolize a drug before it reaches the systemic circulation, leading to low oral bioavailability, which is called the first-pass effect. The benefit of oral administration is that the patient has the ability to self-administer the drug, which is convenient; however the limitations are that some drugs can cause gastrointestinal irritation, drug absorption is not rapid and it may take a longer time for the patient to feel the effect of the drug.

Drugs can be absorbed into the blood stream by several routes of administration. Sublingual route occurs when the drug is placed under the tongue or the buccal route, the drug could be crushed and spread over the buccal mucosa. The advantages are that the drug can be self-administered, drug absorption occurs rapidly and first-pass

drug metabolism by the liver is avoided, which preserves the bioavailability of the drug. The disadvantages could be that the drug may have an unpleasant taste, the drug could irritate the oral mucosa and that large quantities of the drug could not be administered at one time.

Drugs can be administered rectally as a suppository, where the drug can dissolve or becomes a liquid in the rectum. Rectal administration is used in individuals who are unconscious or vomiting. This route can also be used to administer drugs to children and elderly patients. There is minimal to no first-pass liver metabolism. The disadvantages could be that rectal drug administration is uncomfortable or embarrassing for the patient and there is the possibility that the drug can cause irritation or inflammation of the rectal mucosa. In addition, drug absorption is slow and drug bioavailability is inconsistent and less predictable.

Drugs can be administered through the skin for transdermal absorption. Absorption of the drug is depended on the surface area of the skin where the drug is administered, lipid solubility of the drug and blood flow to the skin. Transdermal absorption can be enhanced by placing the drug in an oil and rubbing it on the skin. The advantages to transdermal drug delivery could be a longer duration of drug action, a reduction in the frequency of drug dosing, consistent drug bioavailability.

Intravenous administration provides 100% drug bioavailability and avoids first pass drug metabolism from the liver. It is a quick route to deliver drugs to blood circulation and the patient should achieve the targeted blood concentration for appropriate therapy. Larger doses of drugs can be administered through this route and it eliminates the risk of oral, GI and rectal mucosal irritability or inflammation. In addition, IV administration can be used to provide nutrition, fluids and electrolytes to the patient, for individuals that are unable to take food orally. The disadvantages include the need for a phlebotomist, there is a risk for acquiring an infection and the needle stick could be painful.

Other routes of drug administration include: Parenteral, Subcutaneous, Intramuscular, Intrathecal and Inhalation

Factors that affect Absorption include:

The ability of the drug to be soluble

Patient's physiology and pathology, such as gastric emptying time, gastric pH and comorbidities and the characteristics of the drug, such as molecular weight, concentration, formulation, ionization ability, protein binding and drug transport, which will impact the pharmacokinetics and pharmacodynamics of the drug.

Slide 9: Volume of Distribution

Another term in pharmacokinetics is volume of distribution (Vd), 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 in the body to contain the total amount of drug administered at the same concentration in serum or plasma.

Drug distribution is dependent on 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 Vd 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

So now that our drug has crossed the first set of membranes and is in the 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. Oral drugs undergo first-pass metabolism and lead to a decrease in drug bioavailability.

Drugs administered intravenously will bypass first-pass metabolism in the liver and have 100% bioavailability in systemic circulation.

Factors influencing bioavailability of oral drugs include: drug formulation, interaction with other substances in the GI tract; characteristics of the drug (absorption, biotransformation), characteristics of the patient (GI pH, GI motility, blood perfusion, bacterial flora, malabsorption states, kidney, liver and cardiac function and genotype)

Of note, intermuscular injection of a drug does not guarantee bioavailability because blood perfusion of the muscular site may be low.

Drug bioavailability can be impacted by serum protein binding of drugs to protein carriers, which affect drug distribution into the tissues. The amount of drug available for transport across a membrane depends on the concentration of free, non-bound, drug.

Slide 11: Steady state concentration

Steady state can be defined as the point in which the dose entering the circulation equals the amount being eliminated.

The figure demonstrates a drug that is administered at a fixed dosing interval will accumulate in the body until a steady-state condition exists.

Steady state concentration is achieved when the amount of drug administered at a constant rate, is equal to the amount of drug eliminated from the body

Steady state concentration is achieved after 5-7 half-lives of the drug after it has been administered. For example, if the drug has a half-live of 24h and the drug is

administered once a day, then it will take 5 to 7 days of daily dosing to reach steady state concentration. Therapeutic drug monitoring should be conducted once the patient has reached steady state concentration.

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, and decreases the 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 molecule can be metabolized by phase I reactions, which alter chemical structure by oxidation, reduction, or hydrolysis. Drugs can also be metabolized by phase II reactions, which conjugate the drug to water-soluble forms. Typically, both phase I and phase II reactions occur. Most drug metabolism takes place in hepatocytes, however, metabolism can also occur in other organs.

The role of TDM is important for drugs with variability in the rate of metabolism in different patients of the general population that 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.

Slide 14: Factors that Affect PK and PD

To summarize, TDM results are impacted by factors that affect pharmacokinetics and pharmacodynamics, such as age and gender,

nutrition, pharmacogenetics, body weight, pregnancy, disease, drug-drug and food-drug interactions. 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 pharmacodynamics of the drug. Drug metabolism and elimination can be impacted by age. Children may not have well developed liver function and may not metabolize drugs extensively as 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 15: TDM Workflow

Here is a flowchart to describe the traditional workflow for therapeutic drug monitoring.
A drug test is ordered for routine drug monitoring or to identify issues with drug therapy.
Blood specimens are collected, stored and transported to laboratory
Specimens are processed and tested at the Laboratory
Results are reported
Clinical decision is made for the appropriate treatment dose

Slide 16: Timing of Specimen Collection

Before the patient's specimen is collected, it is important to determine the appropriate timing of specimen collection and the appropriate specimen type.
Accurate timing of sample collection is often an important factor in TDM, especially when timed samples such as peak or pre-dose (trough) samples are the primary means of monitoring.
Drugs with slow distribution and a long half-life, such as digoxin, are optimally sampled in the post-distribution phase of more than 6 hours after dosing. It is important to perform TDM when the patient has reached steady-state concentration.

Of note, a single concentration measurement may not provide sufficient information to determine the adequacy of drug exposure; therefore routine drug monitoring is standard practice for several drugs.

Slide 17: Monitoring of Free (unbound) drug

Once a drug enters the systemic circulation, it distributes and comes to equilibrium with many of the blood components, such as plasma proteins. An equilibrium exists between free and protein-bound drug. It is generally believed that only the free fraction of the drug is available for distribution and elimination. In addition, only the free drug is available to cross cellular membranes or to interact with the drug receptor to elicit a biological response. Therefore changes in the protein-binding characteristics of a drug can have a profound influence on the distribution and elimination of a drug.

Some clinically important aspects of serum protein binding of drugs that should be noted:

- As the free drug concentration decreases, the pharmacologic activity decreases and the drug clearance decreases
- A highly protein bound drug may be competitively displaced by another highly bound drug and the pharmacologic effect of the displaced drug (free, unbound) will increase and the renal clearance will increase.
- In disease states characterized by hypoalbuminemia, the concentration of free drug will be higher at any total concentration. In disease states characterized by increases in acute phase proteins, the free drug concentration will decrease and the pharmacological effect will be decreased.
- Endogenous substances (bilirubin, fatty acids) may also displace a highly bound drug

TDM for free (unbound) drugs should be performed for drugs that are highly-bound (> 80%) to plasma proteins, especially in patients with renal failure, liver disease, patients with low albumin concentrations and for patients in which the drug concentration does not correlate with clinical expectation.

Slide 18: Pre-analytical variables

For TDM to be effective, the drug concentration must be accurate and precise. There are various factors can affect the measurement of drugs in blood. Variations in specimen collection and handling of samples for TDM also can impact the quality of the result. Although serum is the preferred sample for monitoring of many drugs, there are different collection tubes are available that include plastic tubes without additives as well as specialized serum separator tubes that contain a gel to separate serum from the cellular components after centrifugation. Serum separator tubes can affect drug concentration because of adsorption of drug into the gel after prolonged contact. The adsorptive effects can vary among drugs and have been shown to significantly reduce the drug concentration. Therefore, separator tubes should be avoided. The stability of drugs after collection also may vary, and can be impacted by collection tube preservatives, temperature, light, freeze thaw cycles, and interferences, such as lipids, bilirubin and hemoglobin.

Therefore, pre-analytical factors can impact the accuracy and precision of TDM results.

Slide 19: Drug-Drug interactions Affect Efficacy

Drug-drug interactions can also affect drug efficacy. Whenever two or more drugs are being taken, there is a chance that there will be an interaction among the drugs. The interaction may increase or decrease the effectiveness of the drugs or the side effects of the drugs. The types of drug-drug interactions include:

Synergism occurs when two drugs are administered with the same effects and lead to an enhanced response to the drug

Antagonism occurs when two drugs with opposing actions interact and reduces the effectiveness of one or both drugs

Enzyme saturation – this can occur when two drugs are administered and are metabolized by the same CYP450 liver enzyme. This can cause the metabolism of one drug to inhibit metabolism of the other

Slide 20: Drug-drug interaction

Enzyme induction leads to an increase in drug metabolism and decrease drug concentrations in blood. Enzyme inhibition can decrease drug metabolism and may lead to a rise in the drug concentration in blood.

Drugs can also alter how the body absorbs, metabolizes or excretes another drug.

Slide 21: Analytical methods

TDM is beneficial when there is an analytical method available.

Several drugs for TDM can be measured by chromatographic methods or individually analyzed by immunoassay. The advantage of chromatographic methods such as liquid chromatography–tandem mass chromatography is the ability to simultaneously analyze multiple drugs in a single assay and methods typically provide higher specificity for identification of the drug. Immunoassay methods are less labor intensive and have faster turnaround time to result than chromatographic methods for measuring a single analyte. However the limitations of immunoassay methods are that they may lack specificity between parent drug and metabolite and there is a potential for false positive results if there is cross-reactivity with drugs that are structurally similar. Immunoassay methods can be susceptible to inference by bilirubin, lipemia, hemoglobin, paraproteins and heterophilic antibodies.

Of note, analytical methods must be validated or verified before testing patient specimens for TDM.

Slide 22: Summary

- TDM is the practice of individualized drug dosing and should be interpreted with respect to patients' clinical presentation
- TDM results are influenced by:
    - Patient's physiological condition
    - PK, PD, PG
    - Medications
    - Diet / supplements

- Pre-analytical, Analytical and Post-analytical variables
- Analytical methods

Slide 23: References

Slide 24: Disclosures

Slide 25: Thank You from www.TraineeCouncil.org

Thank you for joining me on this Pearl of Laboratory Medicine on "**Therapeutic drug monitoring**."