PEARLS OF LABORATORY MEDICINE

Therapeutic Drug Monitoring

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Learning Objectives

• Discuss the rationale for therapeutic drug monitoring (TDM)

• Describe how drug therapy is impacted by pharmacokinetics, pharmacodynamics and pharmacogenetics

• List various classes of drugs that require TDM

• Discuss analytical methods available for TDM
What is TDM?

• The practice of individualized drug dosing:
  
  • To enhance drug efficacy and reduce the risk of toxicity
  
  • Reserved for drugs with a well-established relationship between blood concentration and clinical effect
  
  • Targeted for drugs with unpredictable pharmacokinetic-pharmacodynamics relationship with dose
  
  • Drugs with a narrow therapeutic index
Therapeutic index = TD50 / ED50

TD50: toxic dose in 50% of subjects

ED50: efficacious dose in 50% of subjects
Indications for TDM

- Monitor patient adherence to prescribed medication
- To ensure that the patient drug concentrations are within the therapeutic range
- Assess toxicity or adverse drug reactions
- Improve patient care through directed decontamination efforts
Recommended Drug Classes for TDM

• Antiarrhythmics
• Antibiotics
• Anti-cancer drugs
• Antidepressants
• Antiepileptics
• Antipsychotics
• Bronchodilators
• Cardiac drugs
• HIV drugs
• Immunosuppressant drugs
• Lithium

THESE ARE GUIDELINES

Actual TDM services should be based on needs of clients and current literature.
Drug Therapy is Impacted by Pharmacokinetics and Pharmacodynamics

- Pharmacokinetics (PK)
  *What the body does to the drug: ADME - evaluated by drug levels*
- Pharmacodynamics (PD)
  *What the drug does to the body: response, mechanism(s) of action evaluated by clinical response, biomarkers*
- Pharmacogenetics (PG)
  How genes affect drug metabolism and clinical effect
Drugs Must Be Absorbed into blood circulation

- Routes of Administration
  - Oral
  - Sublingual
  - Rectal
  - Transdermal
  - Intravenous
  - Parenteral
  - Subcutaneous
  - Intramuscular
  - Intrathecal
  - Inhalation

- Factors that affect Absorption
  - Drug solubility
  - Patient: pathology, gastric emptying time, pH
  - Drug characteristics: polarity, molecular weight, concentration, formulation
    - Ionization
    - Protein binding
    - Drug transport
Volume of Distribution (Vd)

- Describes the amount of drug that enters the plasma compartment, and where it goes in the body.

- Drug distribution is dependent on drug and compartment.
  - Drug
    - polar drugs = water soluble → circulation → kidneys
    - nonpolar drugs = lipid soluble → CNS, tissue, fat → liver/bile
  - Compartment
    - minutes: plasma and well-perfused organs (heart, liver, kidney, brain)
    - minutes to hours: muscle, skin
    - hours to days: fat
Bioavailability (F)

• The amount of drug that reaches systemic circulation
  • Blood concentration of the drug

• Oral drugs – undergo first-pass metabolism → a decrease in bioavailability

• Drugs administered IV – bypass first-pass metabolism → 100% bioavailability

Volume of Distribution (Vd)

• Relates the amount of drug in the body to the concentration of drug in the blood or plasma
Steady state ($C_{ss}$):

amount of drug in = amount of drug out, requires 5-7 $t_{1/2}$
Drug Metabolism

• Purpose – convert drugs into more hydrophilic metabolites to enhance elimination from the body

• Effects
  • Terminates pharmacological activity of drug
  • Activate pharmacological activity of a drug (codeine → morphine)
  • Decreases bioavailability (first pass metabolism)

• TDM tests should measure parent compound and/or metabolites
Drug Metabolism

• Phase I reactions (oxidation, reduction, hydrolysis)
  • cytochrome P450 (CYP3A4/5, 2D6, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1)
  • monoamine oxidase
  • alcohol dehydrogenase
  • dopamine β-hydrolase

• Phase II reactions - conjugations with glutathione, glucuronide, sulfate, methyl group, acetyl group
  • GSTs, UGTs, SULT, MT, TPMT, NAT

• Sites for Drug Metabolism
  • Liver, GI tract, lung nasal mucosa, skin, etc.
Factors that Affect PK and PD

Pharmacokinetics and Pharmacodynamics

- Age and Gender
- Nutrition and Environment
- Diseased
- Infection
- Inflammation
- Drug-Drug or Food-Drug Interactions
- Body Weight and Pregnancy
- Pharmacogenetics
TDM Workflow

1. Test request for TDM
2. Blood specimens are collected, stored, and transported to the laboratory
3. Whole blood, serum, or plasma
4. Specimens are tested at the laboratory
5. Results are reported
6. Clinical decision is made for the appropriate treatment dose
Timing of Specimen Collection

- Specimens – serum/plasma, blood, dried blood spots, oral fluid

- Specimens are drawn at either –
  - Peak, pre-dose (trough), or random
  - Majority of drugs are collected at pre-dose (trough)

- Peak collection (aminoglycosides)
  - Drugs administered intravenously
  - Patient experiences signs of toxicity after dose

- For drugs with a long distribution phase
  - Random specimen is collected
  - Digoxin
Monitoring Free (Unbound) Drug

- Patients with Renal failure
  - Toxins can displace protein-bound drug in uremic patients

- Patients with Liver Disease

- Patients with hypoalbuminemia
  - critically ill
  - burn patients
  - AIDS patients

- Patients where drug concentrations do not correlate with clinical expectation (drug-drug interactions, pregnancy, stress).
Pre-analytical variables

- Hemolyzed specimens
- Clotted specimens
- Interferences –
  - Lipemia
  - Icterus
  - Hemoglobin
- Collection tubes - Avoid gel separator tubes
- Specimen collection conditions
  - preservatives,
  - temperature
  - light
  - freeze/thaw cycles, etc.

Drug-Drug Interactions – Affect Efficacy

- **Synergism** – two drugs are administered with the same effects → response to drug is enhanced

- **Antagonism** – two drugs with opposing actions interact → reducing the effectiveness of one or both drugs

- **Enzyme saturation** – two drugs are administered and are metabolized by the same CYP450 liver enzyme → metabolism of one drug can inhibit metabolism of the other
Drug-Drug Interactions

• Induction – a drug can enhance the metabolism of a drug or its own metabolism
  • (ex. Rifampin (antibiotic) → induces CYP450 2B6, 2C8, 2C9, 2C19, 2D6, 3A4)

• Alteration – one drug may alter how the body absorbs, metabolizes, or excretes another drug
Analytical Methods

- GC-MS
- LC-MS
- HPLC
- Immunoassays
- Spectrophotometry
Summary

- TDM is the practice of individualized drug dosing
  - Should be interpreted with respect to patient’s clinical presentation

- TDM results are influenced by:
  - Patient’s physiological condition
  - PK, PD, PG
  - Concomitant medications
  - Diet / supplements
  - Pre-analytical, Analytical and Post-analytical variables
  - Analytical methods
References

1. Tietz textbook of Clinical Chemistry and Molecular Diagnostics, Sixth edition, Chapter 40 – Therapeutic Drugs and their Management

2. Contemporary Practice in Clinical chemistry, Third edition, Chapters 44 and 45
   - Pharmacokinetics for the Practicing Clinical Chemist
   - Therapeutic Drug Monitoring
Disclosures/Potential Conflicts of Interest

Upon Pearl submission, the presenter completed the Clinical Chemistry disclosure form. Disclosures and/or potential conflicts of interest:

- **Employment or Leadership**: No disclosures
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