Therapeutic Drug Monitoring (TDM)

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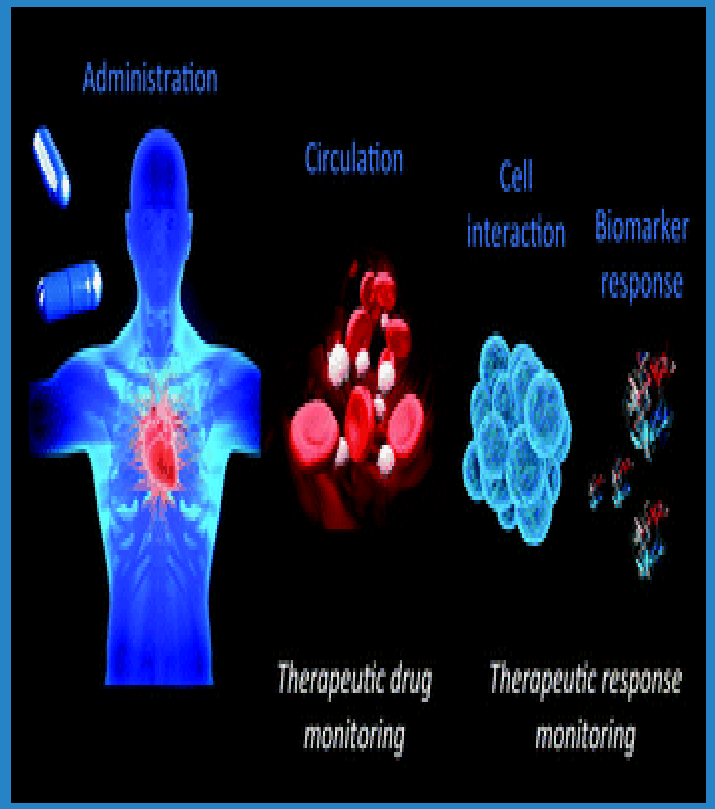
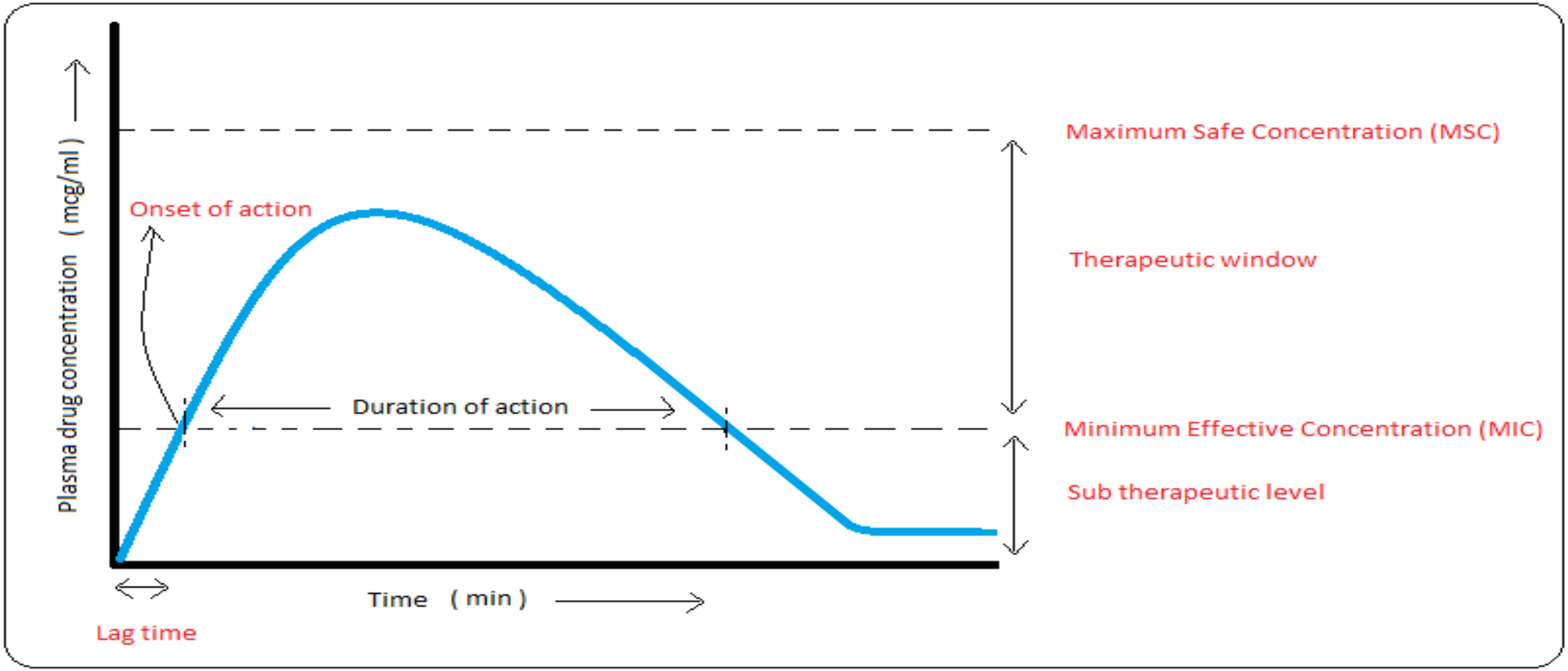
Introduction (TDM)



Therapeutic Drug Monitoring (TDM) is the clinical practice of measuring specific drugs at designated intervals to maintain a constant concentration in a patient's bloodstream, thereby optimizing individual dosage regimens.

In other words, TDM refers to the individualization of drug dosage by maintaining plasma or blood drug concentrations within a targeted therapeutic range or window.

TDM aims to promote optimum drug treatment by maintain serum drug concentration within a 'Therapeutic Range'.


Plasma drug concentration (mcg/ml)
Maximum Safe Concentration (MSC)
Onset of action
Therapeutic window
Duration of action
Minimum Effective Concentration (MIC)
Sub therapeutic level
Time (min)
Lag time

Introduction (TDM)

- Involves the analysis, assessment and evaluation of circulating concentrations of drugs in serum, plasma, or whole blood.
- Purpose is to ensure the medication dose is at therapeutic range and not toxic.
- Medications dosage differ between each patient based on metabolic process.
- Therapeutic range is narrow for some drugs
  - below range: drug not effective
  - above range: drug toxic

Gawade, S. (2016). Overview on Monitoring of Therapeutic Drugs. *Indian Journal of Pharmacy Practice*, 9(3), pp.152-156.

- Clinicians routinely monitor drug pharmacodynamics by directly measuring physiological indices of therapeutic response (E.g.: lipid concentration, blood glucose, BP, clotting test)
- For many drugs there is no readily available measure of effect or it is insufficiently sensitive
- Large interindividual variation between dose and response can make individualizing drug dosage difficult

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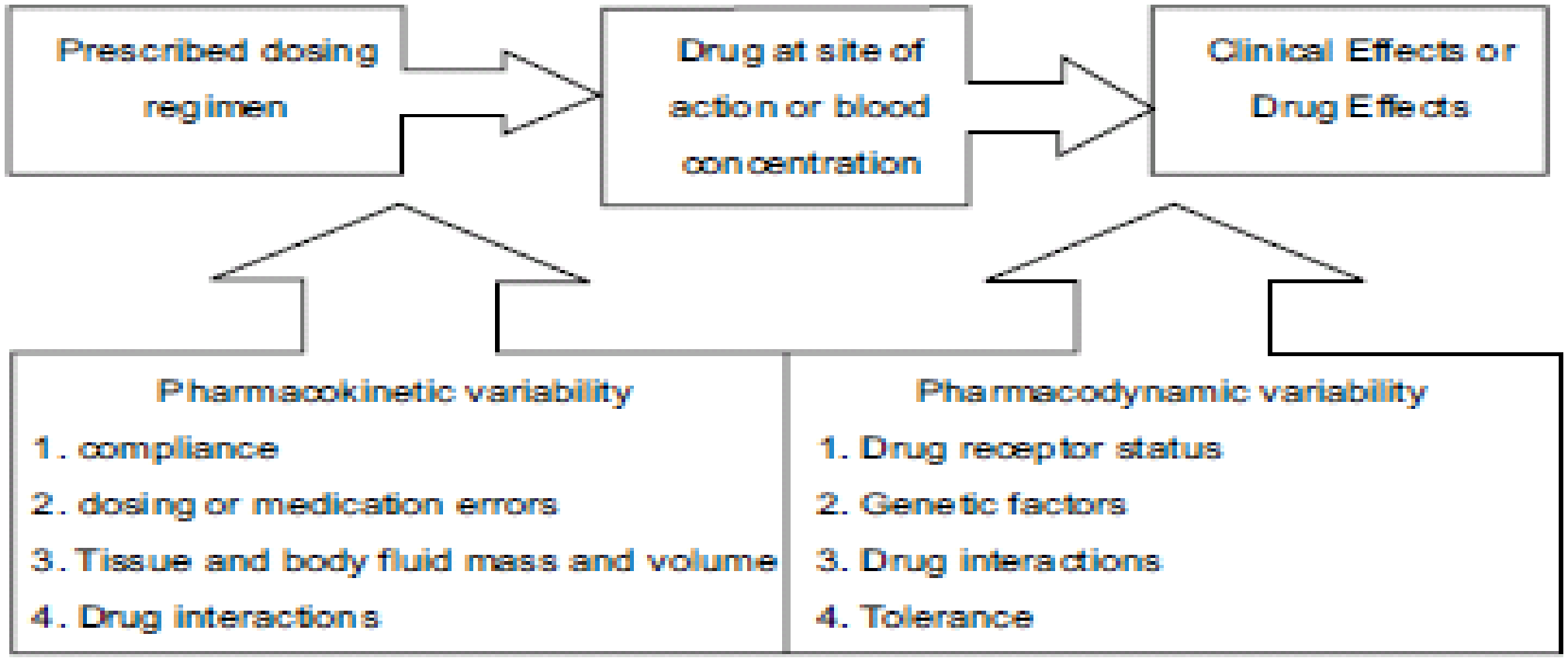
Prescribed dosing regimen
Drug at site of action or blood concentration
Clinical Effects or Drug Effects
Pharmacokinetic variability
1. compliance
2. dosing or medication errors
3. Tissue and body fluid mass and volume
4. Drug interactions
Pharmacodynamic variability
1. Drug receptor status
2. Genetic factors
3. Drug interactions
4. Tolerance

Indications of TDM

- The consequences of overdosing and under dosing are serious.
- There is a small difference between a therapeutic and toxic dose.
- There is a change in the patient's physiologic state that may unpredictably affect circulating drug concentrations.
- A drug interaction may be occurring.
- TDM helps in monitoring patient compliance.

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Therapeutic Drug Monitoring Process

Routes Of Administration

- For a drug to express a therapeutic benefit, it must be at the appropriate concentration at its site of action.
- Measuring drug concentration at the site of action would be ideal.
- Unfortunately, for most drugs, this cannot be done.
- The circulatory system offers a convenient route that can effectively deliver most drugs to its site of action
- The goal of most therapeutic regimens is to acquire a blood, plasma, or serum concentration that has been correlated with an effective concentration at the site of action

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Routes of Administration

Each presents with different characteristics that influence circulating concentrations

1. Orally (most common)
2. Rectally
3. Intravenous (IV)/ intramuscular (IM)
4. subcutaneous
5. Inhalation
6. or absorbed through the skin

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Biological effect

- A drug is effective when it binds to a specific receptor in the target tissue.
- TDM assumes that serum levels are proportional to the intercellular tissue bind capacity of the drug.
- Drug utilization in the body is influenced by:
    1. Absorption
    2. Distribution
    3. Metabolism
    4. Excretion

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Absorption

- The efficiency of drug absorption from GIT is dependent on many factors:
  - Tablets and capsules require dissolution before being absorbed.
  - Liquid solutions are more rapidly absorbed.
  - Weak acids are efficiently absorbed in the stomach.
  - Weak bases are absorbed in the intestine.
  - Changes in intestinal motility, pH, inflammation, as well as food or other drugs may dramatically change absorption characteristics.

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Absorption

- All substances, including drugs, absorbed from the intestine enter the hepatic portal system,
- certain drugs are subject to significant hepatic uptake and metabolism (**first-pass metabolism**)
- this process is known as Characteristics of drug may change in pregnancy, age, etc

❑With the use of TDM, effective dosage treatment can be determined.

Distribution

- Once drug is absorbed into the blood, it begins to distribute to tissues
- The amount of drug that partitions into tissues depends on:
  - Solubility
  - Protein binding
- The partitioning of drug between blood and tissues is expressed quantitatively as the **Volume of Distribution**

Excretion

- Hepatic metabolism or renal filtration, or a combination of the two, eliminates most drugs.
- Functional changes in these organs may result in changes in the rate of elimination.
- **Half-life** represents the time needed for the serum concentration to decrease by one half.

Metabolic Clearance

- Most drugs are **xenobiotics**
  - substances not normally found within human system, yet capable of entering biochemical pathways intended for endogenous substances.
- The biochemical pathway responsible for a large portion of drug metabolism is the hepatic mixed function oxidase "**MFO**" system.

Metabolic clearance

- The basic function of **MFO** system involves taking hydrophobic substances and through a series of enzymatic reactions converting them into water-soluble substances.
- These products are then either pumped into the bile or released into the general circulation, where they are eliminated by renal filtration.

Excretion - Renal

- Kidneys are the primary excretory organ.
- In Renal disease
  - other excretory organs or pathway become involved such as: biliary tract, lungs and sweat glands.
- Water soluble drugs excrete faster than insoluble.
- Decreases in glomerular filtration rate directly results in increased serum half-life and concentration

TDM will be Useful If…

1. The drug in question has a narrow therapeutic range
2. A direct relationship exists between the drug or drug metabolite levels in plasma and the pharmacological or toxic effects
3. The therapeutic effect can not be readily assessed by the clinical observation
4. Large individual variability in steady state plasma concentration exits at any given dose
5. Appropriate analytic techniques are available to determine the drug and metabolite levels

TDM is Unnecessary If…

6. Clinical outcome is unrelated either to dose or to plasma concentration
7. Dosage need not be individualized
8. The pharmacological effects can be clinically quantified
9. When concentration effect relationship remains unestablished
10. Drugs with wide therapeutic range such as beta blockers and calcium channel blockers

CRITERIA FOR TDM

1. Assay methods
2. Narrow therapeutic range
3. Poor relationship between dose and serum drug concentrations (SDC)
4. Non-linear pharmacokinetics
5. Good relationship between serum SDC and therapeutic/toxic effects
6. Lack of therapeutic effects is dangerous
7. Difficulty in interpreting signs and symptoms of toxicity or therapeutic failure or in evaluating therapeutic responses

a. Toxicity vs therapeutic failure

b. Therapeutic responses

TDM ASSAY METHODOLOGIES

1. EMIT: highly automated, rapid turnaround, many assays available, homogenous, moderate sensitivity but poor stability of calibration curve
2. ELISA: highly automated, rapid turnaround, moderate sensitivity but few assays available, heterogenous
3. RIA: high sensitivity but long turnaround,many interferences, heterogenous, radiation hazards
4. FPIA: highly automated, rapid turnaround, many assays available, stability of reagents and calibration curves, moderate sensitivity, homogenous
5. HPLC: highest sensitivity, most assays available, least expensive but long turnaround, requires highly trained personnel

TYPES OF ASSAY REQUIRED

- **Total drug conc.**
- **Free drug conc.**
- **Metabolites**

APPROPRIATE USE OF TDM

1. Maximizing & speeding up efficacy
2. Minimizing toxicity
3. Patient's drug history uncertain
4. Poor response to initial Rx or deterioration after good response
5. When hepatic or renal function is changing
6. During drug interactions
7. Individualizing therapy and dosage regimen adjustment
8. To make decision about future therapy
9. Pharmacokinetic profiling

FACTORS AFFECTING SDC & INTERPRETATION OF SDC

1. Disease states: renal, liver, cardiac, thyroid
2. Habits: diet, smoking, drinking
3. Pregnancy, age, weight
4. Non-compliance
5. Electrolyte balance : Digoxin vs K^{+} & Ca^{++}
6. Drug interactions
7. Plasma protein binding
8. Bioavailability
9. Sampling time

GUIDELINES FOR SAMPLING TIME

- Establish that SDC is at steady-state
- Ensure complete absorption and distribution
- Reasons for TDM
  - All except aminoglycosides
    - suspect toxicity - peak SDC
    - suspect failure or noncompliance - trough SDC
  - Aminoglycosides
    - suspect toxicity - peak & trough SDC
    - suspect failure or noncompliance : peak SDC

CLINICAL USEFULNESS OF TDM

MAXIMIZING EFFICACY

- Epileptic pt. vs Phenytoin
- Burn pt. vs Gentamicin
- Asthmatic pt. vs Theophylline
- Life-saving in serious situations

CLINICAL USEFULNESS OF TDM (cont'd)

AVOIDING TOXICITY

- Overdose
- Differentiate adverse effects from disease states
  - Digoxin toxicity vs ventricular arrhythmias
  - Digoxin toxicity vs hypo-K or hyper-Ca
- Altered pharmacokinetics

CLINICAL USEFULNESS OF TDM (cont'd)

IDENTIFYING THERAPEUTIC FAILURE

- Non-compliance
- Subtherapeutic dose
- Bioavailability problem
- Malabsorption
- Drug interactions

CLINICAL USEFULNESS OF TDM (cont'd)

FACILITATING ADJUSTMENT OF DOSAGE

New dose = Old dose X Desired C_{ss}/Old C_{ss}

Clearance : obtain a C_{ss}

MD = Css X Cl

$T_{1/2}$ or Dosing interval : obtain a peak

& trough

CLINICAL USEFULNESS OF TDM (cont'd)

FACILITATING THERAPEUTIC EFFECTS

- **Target drug conc.: Antiepileptics**
- **Dosage adjustment**

Drugs commonly measured

A. Cardiac medications (digoxin)
B. Antibiotics (amikacin, gentamicin, vancomycin)
C. Antiepileptic drugs (phenobarbital)
D. Psychoactive Drugs (lithium)
E. Immunosuppressants (Cyclosporine)
F. Antineoplastic (Methotrexate)

Sample Collection

- For most drugs, sample is collected right before the next dose.
- Peak concentrations are drawn 1 h after an orally administered dose.
- Some drugs "e.g digoxin" are absorbed slowly and require several hours before peak drug levels can be evaluated.
- In all situations, determination of serum concentrations should be done only after steady state has been achieved.
- Serum or plasma is the specimen of choice for most drugs.

A. Cardiac medication

Medication that is used to treat various heart diseases.

1. Digoxin:

- cardiac glycoside used for CHF.
  - Function by inhibiting membrane Na, K, ATPase pump.
  - ↓ intracellular K^+ → ↑ Ca^{++}
  - improves cardiac contraction.

A. Cardiac medication- Digoxin

- ↑ conc. → toxic effects include:
  - premature ventricular contractions "PVCs"
  - and atrioventricular node blockage
- Therapeutic range: 0.8-2 ng/mL
- Absorption orally is variable and is influenced by dietary factors and formulation of the drug
- Elimination occurs by renal filtration

Digoxin is measured in serum using immunoassay.

A. Cardiac medication

2- Lidocaine

Used to correct ventricular arrhythmias and prevent ventricular fibrillation.

Completely eliminated by the liver if orally given as monoethylglycinexylidide (MEGX).

Therapeutic range: 1.5 - 4.0 µg/ml

Toxic effects include CNS depression

B. Antibiotics

1. **Aminoglycosides:**
   - treat infection with gram negative bacteria.
   - Gentamycin, tobramycin, amikacin, and kanamycin
   - Therapeutic range 4 - 10 μg/mL
   - Toxicity involve; nephrotoxicity and ototoxicity (ear) and effects balance and hearing.
   - Eliminated by renal system
   - Chromatography and immunoassay

B. Antibiotics

2. Vancomycin

- Glycopeptides: effective against Gram positive cocci and bacilli.
- Poor oral absorption, given IV.
- Therapeutic range: 5-10 µg/ml
- Toxicity: kidney, ototoxicity, Red-man syndrome(flushing of skin of the extremities)
- Eliminated by renal excretion
- It is assayed by immunoassay and chromatographic methods.

C. Antiepileptic drugs

- Used to treat epilepsy seizures and convulsions on a prophylactic bases.

Phenobarbital:

- is a barbiturate that is absorbed slowly orally and has a long half-life.
- Primidone is its preform (inactive)- rapidly absorbed and converted into the active form.
- Therapeutic range: 15 - 40 ng / ml
- Toxicity: drowsiness, fatigue and depression

D. Psychoactive Drugs

Lithium:

- Used to treat manic-depression (bipolar disorder).
- Absorption is complete and rapid.
- Distribution is uniform throughout the body.
- Eliminated by renal function.
- Therapeutic range: 0.8 – 1.2 mmol/l
- Toxicity: cause apathy, speech difficulty's and muscle weakness.

E. Immunosuppressive drugs

- Used to prevent rejection in various organ transplantation procedures.

Cyclosporin:

- cyclic polypeptide used to prevent GVHD.
- It is eliminated by hepatic metabolism to inactive products.
- The dose is dependent on the organ transplanted, cardiac, liver, or pancreas transplants

Cyclosporin:

- Toxic effects when blood concentration ranges from 350-400 ng/ml.
- Toxic effects are primarily renal tubular and glomerular dysfunction.
- Determination using immunoassays and chromatographic methods.

F. Antineoplastic

- Used to treat neoplastic disorders (cancer)

Methotrexate:

- inhibits DNA synthesis in all cells.
- Neoplastic cells, as a result of their rapid rate of division,
  - have a higher requirement for DNA
  - and are susceptible to deprivation of this essential constituent before normal cells.

Methotrexate:

- The efficacy of therapy is dependent on a controlled period of inhibition, one that is selectively detrimental to neoplastic cells.
- This is accomplished by the administration of **leucovorin**, which reverses the actions of methotrexate at a specific time after methotrexate infusion.
- This is referred to as **leucovorin rescue**.

Methotrexate:

- Failure to stop methotrexate actions results in cytotoxic effects to most cells.
- Evaluation of serum methotrexate concentration, after the inhibitory time period has passed, is used to:
  - determine how much leucovorin is needed to counteract many of the toxic effects of methotrexate.

Thank You!!