Therapeutic Drug Monitoring

Elective 2.3 (2018-19)
Introduction to Pharmacology - Kinetics

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OBJECTIVES

- Definition.
- Rationale of TDM
- Indications of therapeutic drug monitoring
- Clinical significance of Therapeutic drug monitoring
- Application of therapeutic drug monitoring
- Advantages of TDM
OVERVIEW: Use of drug conc in body fluids as an aid to management of drug therapy for cure, alleviation or prevention of disease.

- TDM
  - Response
    - Clinical
    - Lab
    - Prophylaxis of Seizures
    - Irreversible delayed onset of toxic effects
  - Not observable
If the clinically accepted range of Phenytoin is 5 – 20 mg/L
A retrospective survey carried out at the Massachusetts General Hospital showed that whilst prior to the use of digoxin monitoring 13.9% of all patients receiving this drug showed evidence of intoxication, following introduction of monitoring this fell to 5.9%.
A significant difference with regard to length of stay in the hospital between patients on gentamicin who were monitored and their dosage regulated consequently versus those who were not (DeStache, 1990).
The complex nature of the pharmacologic aspects of cancer therapeutics has become more apparent in the past several years with the arrival of a cascade of target-based agents and the difficult challenge of bringing individualized precision medicine to oncology.

Interpatient variability in drug action, singularly in novel agents, is in part caused by pharmacogenomic (PG), pharmacokinetic, and pharmacodynamic (PD) factors, and drug selection and dosing should take this into consideration to optimize the benefit for our patients in terms of antitumor activity and treatment tolerance.

In this regard, somatic genetic evaluation of tumors is useful in not only predicting response to initial targeted therapies but also in anticipating and guiding therapy after the development of acquired resistance; therapeutic drug monitoring of novel small molecules and monoclonal antibodies must be incorporated in our day-to-day practice to minimize the negative effect on clinical outcome of interindividual variability on pharmacokinetic processes of these drugs for all patients, but especially for fragile patient populations and those with organ dysfunction or comorbidities.

For these populations, incorporating frailty assessment tools into trials of newer agents and validating frailty-based dose adjustment should be an important part of further drug development.

“There is accumulating evidence for potential benefits of therapeutic drug monitoring (TDM) in the treatment of cancer with tyrosine kinase inhibitors (TKIs). Relationships between exposure and response (efficacy/toxicity) have been established for several TKIs. For example, the pharmacokinetic targets for efficacy of Imatinib, Sunitinib and Pazopanib have been defined as trough plasma concentrations ($C_{\text{trough}}$) of $>$1,000, $>$50 and $>$20,000 ng/mL for selected indications, respectively.

Dose adjustment based on pharmacokinetic targets could therefore increase response rates and duration.

Furthermore, with appropriate target concentrations defined, excessive side effects in patients using the current fixed dosing strategy may be prevented.”

Modern development trends in psychiatry incorporate greater care for patients and above all individualization of therapeutic approaches.

**Therapeutic drug monitoring (TDM) for phenotyping and genotyping of drug metabolism are possible determinants of improved treatment efficacy, reduced adverse effects of psychotropic drugs, and enhanced treatment compliance**

Plesničar BK¹, Plesničar A. *Therapeutic drug monitoring and pharmacogenetics--is this a way towards creative psychopharmacotherapy?* Psychiatr Danub. 2014 Jun;26(2):96-9.
**THERAPEUTIC DRUG MONITORING (TDM)**

- TDM is measurement of drug conc in blood or plasma that facilitates adjustment of dosage to produce a desired response.

- The aim of TDM is to achieve maximum therapeutic benefit from a drug with minimum unwanted effects.

- Therapeutic drug monitoring can guide clinician to provide effective and safe drug therapy in an individual patient using serum drug concentration.
C. Neef’s Definition of TDM

Therapeutic drug monitoring is a system of quality assurance of a drug management system, aiming that the

RIGHT DRUG is given to
RIGHT PATIENT in
RIGHT DOSE in order to obtain the right effect.
WHAT IS THERAPEUTIC DRUG MONITORING

Therapeutic drug monitoring (TDM) involves tailoring a dose regimen to an individual patient, by maintaining plasma or blood concentrations within a particular range (therapeutic range or therapeutic window).
ADAPTIVE CONTROL

Patient

Population pharmacokinetic values

Initial dose

Measuring concentration

Individual pharmacokinetic values

Adjust the dose
WHY SHOULD DRUG LEVEL BE MONITORED

- Certain drugs have a narrow therapeutic range.
- In concentrations above the upper limit of the range, the drug can be toxic.
- In concentrations below the lower limit of the range, the drug can be ineffective.
- Not all patients have the same response at similar doses
The therapeutic range/therapeutic window is the concentration range of drug in plasma where the drug has been shown to be efficacious without causing toxic effects in most people.
Therapeutic window

- Drug Effect ($C_p$)
- Peak effect
- Onset of effect
- Duration of action
- MEC for adverse response
- Therapeutic window
- MEC for desired response
- Lag period
- Time
WHERE TO FIND INFORMATION REGARDING THERAPEUTIC RANGE

- Recommended therapeutic ranges can generally be found in the product inserts for drugs that require monitoring.
- They are also available in books such as the Physicians Desk Reference, and articles in the primary medical journals.
**DIGOXIN**

- Plasma concentration – response relationship
  - 0.5 µcg/L: No therapeutic effect
  - 0.7 µcg/L: some ↑ in force of contraction of heart
  - 0.8 - 2 µcg/L: Optimum therapeutic range
  - 2 -2.5 µcg/L: ↑ risk of toxicity although tolerated in some patients
  - > 2.5 µcg/L: Gastrointestinal, cardiovascular and CNS toxicity
THEOXYLLINE

- Plasma concentration response relationship
  - < 5mg/L: No bronchodilation
  - 5-10 mg/L: Some bronchodilation and possible anti-inflammatory action
  - 10-20 mg/L: optimum bronchodilation, minimum side effects
  - 20-30 mg/L: increased incidence of nausea, vomiting and cardiac arrhythmias
  - > 30 mg/L: cardiac arrhythmias & Seizures
LITHIUM

- Plasma concentration response relationship
  - < 0.4 mmol/L: Little therapeutic effect
  - 0.4 to 1 mmol/L: Optimum range for prophylaxis of mania
  - 0.8 to 1.2 mmol/L: Optimum range for acute mania
  - 1.2 to 1.5 mmol/L: Causes possible renal impairment
  - 1.5 to 3 mmol/L: Renal impairment, weakness, drowsiness, thirst and diarrhoea
  - 3 to 5 mmol/L: Confusion, spasticity, convulsions, coma and death
PHENYTOIN

- < 0.5 mg/L: No therapeutic effect
- 5 to 10 mg/L: Some anti-convulsant action
- 10 to 20 mg/L: optimum concentration for anticonvulsant effect
- 20-30 mg/L: Nystagmus, blurred vision
- >30 mg/L: Ataxia, drowsiness, coma
Drugs with steep dose response curve for which a small increase in dose can result in a marked increase in desired or undesired response.
TDM WILL BE USEFUL IF

- The drug in question has a narrow therapeutic range.
- A direct relationship exists between the drug or drug metabolite levels in plasma and the pharmacological or toxic effects.
- The therapeutic effect cannot be readily assessed by the clinical observation.
- Large individual variability in steady state plasma concentration exists at any given dose.
- Appropriate analytic techniques are available to determine the drug and metabolite levels.
TDM IS UNNECESSARY WHEN

- Clinical outcome is unrelated either to dose or to plasma concentration.
- Dosage need not be individualized.
- The pharmacological effects can be clinically quantified.
- When concentration effect relationship remains unestablished.
- Drugs with wide therapeutic range
TDM INDICATION FOR DRUGS

The main reasons for measuring drugs in plasma may be summarized as:
(a) To ensure that sufficient drug is reaching the drug receptor to produce the desired response (which may be delayed at onset)
(b) To ensure that drug (or metabolite) concentrations are not so high as to produce symptoms or signs of toxicity
(c) To guide dosage adjustment in clinical situations in which the pharmacokinetics are changing rapidly (eg, in neonates, children or patients in whom hepatic or renal function is changing)
(d) To define the pharmacokinetic parameters and concentration-effect relationships of new drugs

- Low therapeutic index.
- Non compliance.
- Therapeutic failure.
- Drugs with saturable metabolism.
- Wide variation in metabolism of drugs.
- Major organ failure.
- Prevention of adverse drug effects.
- Poorly defined clinical end point.
APPLICABILITY OF THERAPEUTIC RANGES

- Therapeutic ranges are recommendations derived by observing the clinical reactions of a small group of patients taking the drug.
- The lower limit (trough) is set to provide ~50% of the maximum therapeutic effect, while upper limit (peak) is defined by toxicity, not therapeutic effect.
- Therefore **some patients may achieve therapeutic effects at levels below the established range, while some may experience toxicity while still in the established range**
FACTORS THAT AFFECT RESULTS

- Pharmacokinetics
- Pharmacodynamics
- Dose
- Sampling time and type
- Testing methodology
- Genetic polymorphisms
Pharmacokinetic Variability

GENETIC CONSTITUTION

- Smoking
- Tobacco or Marijuana
- Age
- Sex
- Pregnancy
- Lactation
- Exercise
- Sunlight
- Barometric Pressure
- Disease
- Infection
- Immunization
- Occupational Exposures
- Cardiovascular Function
- Dietary Factors Seasonal Variations
SOURCES OF PHARMACOKINETIC VARIABILITY

- Lack of Patient Compliance
- Age – neonates, children, elderly
- Physiology – pregnancy
- Disease – hepatic, renal, cardiovascular, respiratory
- Drug-to-drug interactions
FACTORS THAT AFFECT INTERPRETATION

- Vary from drug to drug. Steady state must be reached before meaningful TDM is possible for those drugs.
- Digoxin concentration must be interpreted in light of creatinine & K+ conc, presence of acidosis
- When determining appropriate lithium dose or interpreting lithium results, knowing if a women is pregnant is key, as dose requirements increase due to increased renal clearance
- Turn around time - Is also important to ensure that the physician has time to evaluate the result before the patient is scheduled to receive his next dose.
SAMPLE INFORMATION REQUIRED FOR ACCURATE INTERPRETATION

- Time of sample in relation to last dose.
- Duration of treatment with the current dose.
- Dosing schedule.
- Age, gender.
- Other drug therapy.
- Relevant disease states.
- Reason for request (e.g. lack of effect, routine monitoring, suspected toxicity)
COMMONLY MONITORED DRUGS

1. Bronchodilators
   Theophylline

2. Antibiotics: aminoglycosides
   Gentamicin, Amikacin

3. Immunosuppressants
   Cyclosporine

4. Anticancers
   Methotrexate

5. Antiepileptics
   Phenobarbital, phenytoin,
   Carbamazepine, valproate

6. Cardiac Drugs
   Digoxin, Procainamide,
   Lidocaine

7. Psychoactive Drugs
   Lithium, TCA

8. Analgesics
   Aspirin, Paracetamol
DO ALL DRUGS NEED TDM?

Drugs that do not need TDM:

- Drugs that used for treating diseases of which their clinical end points can easily be monitored like BP, HR, cardiac rhythm, blood sugar, blood cholesterol and triglycerides, urine volume, body temperature, inflammation, pain, headache, etc.
Response can be measured like BP. Response can be monitored by investigations like APTT. Response can not be detected by clinical response: prophylaxis of seizures or mania. Toxic effects cannot be detected until severe and irreversible like aminoglycosides and immunosuppression.

Dose individualization becomes difficult but is important.
Therapeutic Drug Monitoring

- Starts with a clinical question
- Continues by devising a sample strategy to answer clinical question
- Determines one or more drug concentrations.
- Interprets the results
Laboratory measurement

- Specific methods:
  1. Colorimetry
  2. UV-spectrometry
  3. Fluorescence spectrometry
  4. Chromatography
     a) Gas chromatography
     b) HPLC
     c) HPTLC
     d) SFC
  5. Capillary electrophoresis

6. Immunoassay
   i) RIA
   ii) Enzyme Immunoassay:
       a) ELISA: Enzyme linked immunoassay
       b) EMIT: Enzyme multiplies immunotechnique
       c) FPIA: Fluorescence polarization
       d) NIIA: Nephelometric inhibition

7. LC-MS: Least count mass spectrometry
CLINICAL USEFULNESS OF TDM

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

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 & COST-BENEFITS OF TDM

IDENTIFYING THERAPEUTIC FAILURE

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

HOSPITAL

- Reduce hospital congestion
- Increase quality of Rx and service
- Economic consideration
- Medico-legal aspects
# BENIFITS OF TDM - COST-EFFECTIVENESS OF METHODOLOGY

## PATIENT CARE
- Decrease duration of stay in hospital
- Receive safer and more effective Rx
- More economic
- Increased productivity
- Improve quality of life

## Economic consideration
- Building cost
- Maintenance costs of equipment
- Equipment depreciation costs
- Medical supplies
- Salaries
CAN DRUG CONCENTRATION IN OTHER FLUIDS OF BODY BE MEASURED

- Yes
  - Urine: benzodiazepines
  - Sweat: cocaine & heroin
  - Saliva: marijuana, cocaine, alcohol
  - Breath: alcohol

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SUMMARY

- TDM is monitoring of plasma concentration of drug for individualization of dose in patients
- Mainly indicated for drugs having narrow therapeutic index, or to check compliance and titration of dose
- Most common drugs to undergo TDM are anticonvulsants, lithium, digoxin, gentamicin
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