Therapeutic Drug Monitoring (TDM)

Defn

- TDM refers to the measurement of drug conc. in biological fluids (blood/plasma) with the purpose of optimizing patient's drug therapy and clinical outcome while minimising the risk of drug induced toxicity

TDM

- Analytics –it’s pharmacy
- Result interpretation and dosage schedule suggestion –it’s clinical pharmacy

Therapeutic Drug Monitoring

- TDM refers to the tool utilised to individualize dosage regimen by maintaining plasma/ blood drug concentrations within therapeutic range
- Relates concentrations of drug in blood to response
- Blood concentrations surrogate for the concentration at the site of action
- Principle - concentration correlates better than the dose with the drug effect
- Is important when
  - the dose cannot be titrated against response eg INR
  - the drug is being used to prevent infrequent occurrences - eg epilepsy

Need / Indications for TDM

- Drugs with narrow TI
- Drugs with non linear p'kinetics
- Drugs with large p'kinetic variability
- Drugs in which therapeutic effect is difficult to monitor
- To optimize drug therapy
- Toxicology

Conditions that must be met

- Blood concentrations can be accurately reliably and economically measured
- There is sufficient inter-individual variation in drug handling to warrant individualization of dose
- There is a clear relationship between concentration and beneficial and/or adverse effects, particularly if there is a narrow therapeutic index
- The effects are due to the parent drug and not its metabolites

Monitoring drug therapy

1. By Clinical Response
   - Frusemide:- Heart Failure
     - high dose: Dehydration low dose: ↑Oedema
     - toxic effect: Severe hypotension

2. By an *in vitro* Test of Therapeutic Effect
   - Warfarin: TE disease
     - low dose: high INR high dose: low INR
     - toxic effect: Bleeding
   - Thyroxine: Hypothyroidism
     - low dose: low TSH
     - toxic effect: Hyperthyroidism

3. By a target concentration strategy provided …
   - Drug level quantitatively correlates with therapeutic & toxic effects.
   - High risk of therapeutic failure (lack of response or toxicity)

Monitoring drug therapy

- Therapeutic failure usually arises if the drug has:

  1. A low therapeutic index
  2. Highly variable pharmacokinetics due to
     - saturable elimination
     - genetic factors (poor metabolisers)
     - concurrent disease
     - multiple (and interacting) drug therapies

- Compliance must be confirmed in all cases of therapeutic failure

Purpose of TDM

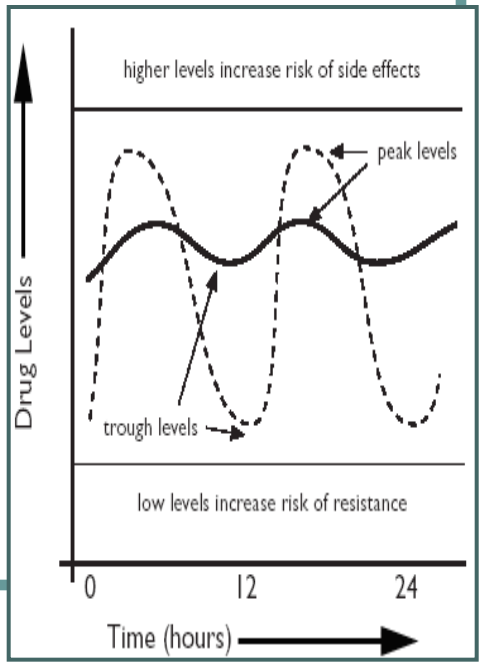
- To confirm ‘effective’ concentrations
- To investigate unexpected lack of efficacy
- To check compliance
- To avoid or anticipate toxic concentrations
- Before increasing to unusually large doses- dose adjustment
- To individualize dosing for some drugs
- Minimize time period for dose adjustment
- Role in toxicology – monitoring efficacy of antidotes and elimination of toxins

The Biological Sample

- Venous blood
- Collection after SS concentration has been achieved
- Loading dose??
- Second loading dose due to poor therapeutic response
- Drugs with short half lives- Trough samples
- Drugs with long half lives- post distribution phase, SS
- IV administered drugs
- Interaction of interference from external sources (lithium heparin as anticoagulant)

Factors affecting serum drug concentrations

1. Patient demographics:
    1. *Age, gender, bw for renally cleared drugs → allows for calculation of creatinine clearance*
    2. *Ethnicity for hepatically cleared drugs*
2. Dosage regimen and duration of therapy
3. Sampling time: *loading dose, half life of drug, trough sample*
4. Patient compliance
5. Individual capacity for drug elimination
6. Altered protein binding
7. Drug interactions
8. Pathological factors
9. Alcohol & tobacco use
10. Medication & sampling errors
11. Laboratory errors: Use of lithium heparin



Potential for Error When Using TDM

- Assuming patient is at steady-state
- Assuming patient is actually taking the drug as prescribed
- Assuming patient is receiving drug as prescribed
- Not knowing when the drug concentration was measured in relation to dose administration
- Not considering drug interactions

Factors affecting plasma levels for Aminoglycosidic antibiotics

Factor	Effect(s)
Renal function	Plasma levels increase as renal functions get impaired.
Age	Elimination and clearance of aminoglycosides decrease with increasing age; therefore, plasma concentrations increase with increasing age.
Distribution Volume	Aminoglycosides distribute primarily to the extracellular fluid compartment which approximates 20-25% of body weight. When volume of distribution decreases, the elimination rate increases and the half-life decreases and vice versa.
Ideal body weight	The drug's distribution volume increases with increasing excess weight, presumably due to distribution into extracellular water within the adipose tissue.

Factors affecting plasma levels for Aminoglycosidic antibiotics

Gender	Elimination rate for gentamicin is faster in females than in males.
Obstetric patients	The extracellular fluid compartment, total body water, cardiac output, renal flow and glomerular filtration are all increased during the later phases of pregnancy and may cause an increase in the elimination rate of aminoglycosides.
Burn patients	Haemodynamic changes, secondary to burn (burn patients are hypermetabolic), appear to explain why these patients have an extremely rapid rate of aminoglycoside elimination. After post burn diuresis, the volume of distribution returns to normal.
Ascites	Patients with ascites have an extremely high distribution volume and thus have a prolonged half-life, even though renal function tests are normal.

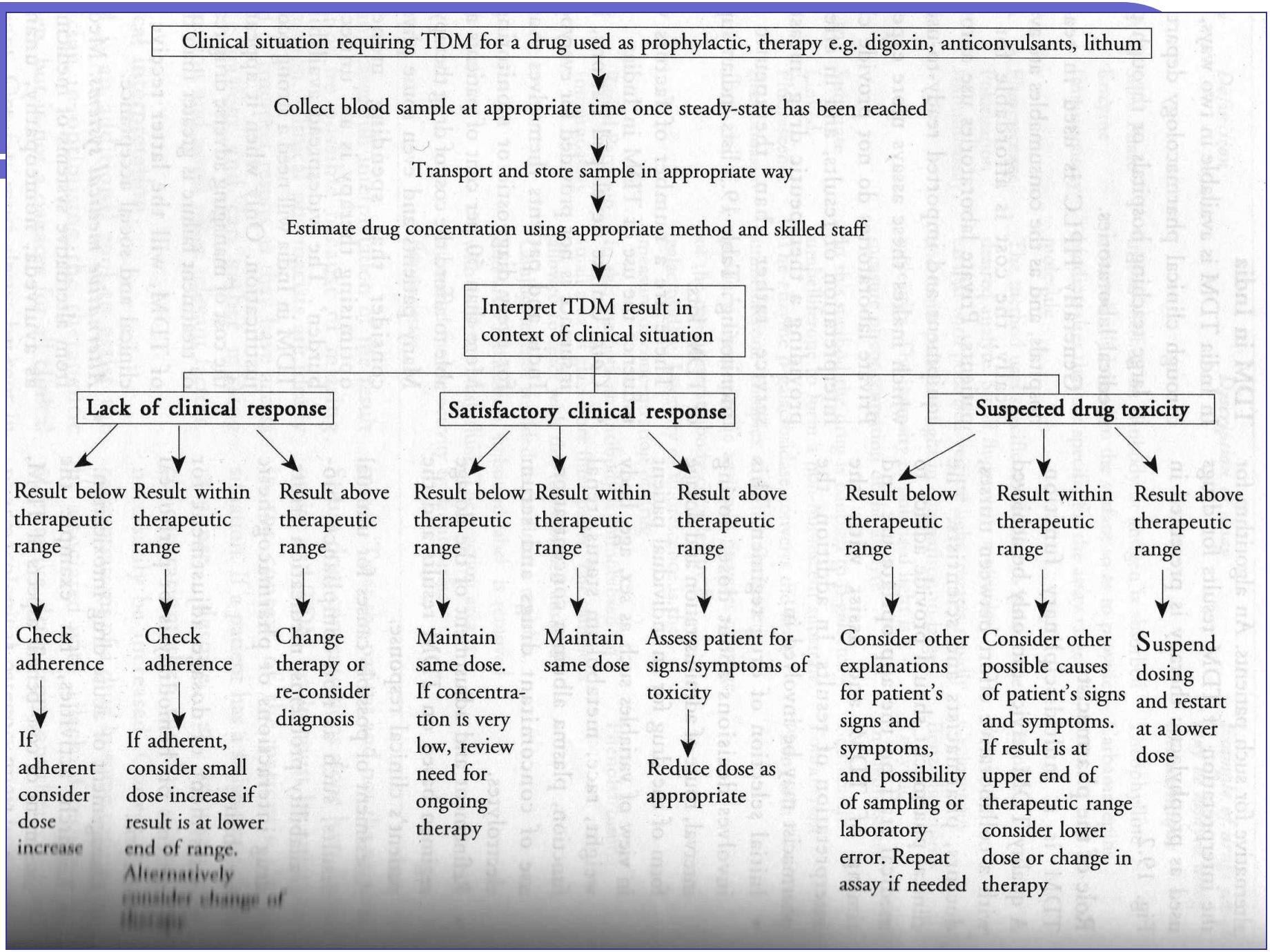
Geriatric	Elderly patients have a progressive decrease in glomerular filtration rate with increasing age. However, serum creatinine may be a misleading indicator of glomerular filtration and aminoglycoside elimination since the endogenous production of creatinine decreases with increasing age.
Surgery/ Critically ill	A wide interpatient variation exists among surgical patients who develop gram-negative sepsis. Surgical patients with infections have many underlying medical complications that may alter the elimination rate of aminoglycosides. Also, critically ill patients may have early signs of organ failure or may inverse be hypermetabolic.
Cystic fibrosis	Patients with cystic fibrosis are hypermetabolic and have higher glomerular filtration rate; therefore, they eliminate aminoglycosides very rapidly.
Neonates	The newborn, specially the premature patient, experience very dynamic changes in physiologic parameters such as cardiac output, renal blood flow, renal function and extracellular fluid. Consequently, the distribution volume, clearance and half-life vary substantially from day to day, and therapeutic concentrations are extremely difficult to attain and maintain.
Gonorrhoea	The elimination rate of aminoglycosides with gonorrhoeic infections is generally rapid and dosage requirements are generally increased in this group of patients.

Quality Assurance in Labs

- Labs are accredited
- Quality assurance programme

Communication & Clinical Interpretation of TDM results

- Results should be communicated as quickly as possible
- Report should incorporate
  - Dosing and sampling details
  - Target concentration ranges
  - Therapeutic ranges
    - Amiodarone: 1- 2.5 mg/l ventricular tachyarrhythmia
      0.5 -1.5 mg/l atrial fibrillation
- Treat the patient not the number
- Important: Correlation of clinical picture & TDM report


Clinical situation requiring TDM for a drug used as prophylactic, therapy e.g. digoxin, anticonvulsants, lithum
Collect blood sample at appropriate time once steady-state has been reached
Transport and store sample in appropriate way
Estimate drug concentration using appropriate method and skilled staff
Interpret TDM result in context of clinical situation
Lack of clinical response
Satisfactory clinical response
Suspected drug toxicity
Result below therapeutic range
Result within therapeutic range
Result above therapeutic range
Result below therapeutic range
Result within therapeutic range
Result above therapeutic range
Result below therapeutic range
Result within therapeutic range
Result above therapeutic range
Check adherence
Check adherence
Change therapy or re-consider diagnosis
Maintain same dose. If concentration is very low, review need for ongoing therapy
Maintain same dose
Assess patient for signs/symptoms of toxicity
Consider other explanations for patient's signs and symptoms, and possibility of sampling or laboratory error. Repeat assay if needed
Consider other possible causes of patient's signs and symptoms. If result is at upper end of therapeutic range consider lower dose or change in therapy
Suspend dosing and restart at a lower dose
If adherent consider dose increase
If adherent, consider small dose increase if result is at lower end of range. Alternatively consider change of therapy
Reduce dose as appropriate

Role of Pharmacist

- Initial selection of drug regimen
- Refinement and adjustment of dosage
  - Cases of hepatic and renal dysfunction
- Assessing causality of unusual results
  - Noncompliance, BA problems, medication errors, DIs, pharmacogenetic variablity
- Management of acute drug intoxication
- Assessment of dosage adjustment in cases of hepatic or renal dysfunction
- Research activities: Pharmacoeconomics

TDM in India:Challenges

- Cost
- Alternative medical systems
- Malnutrition: Low protein
- Ethnic differences
- Variability in BA

TDM - examples

- Lithium - used for bipolar disorder
- Toxic - neurological, cardiac, renal
- Narrow therapeutic range:
  - 0.8 - 1.2 mmol/L acutely
  - 0.5 - 0.75 mmol/L for maintenance
  - Chronic concentrations of 3.0 are potentially lethal
- Renal clearance of Li can be affected by diuretics and NSAIDs

Anticonvulsants

- Variable dose dependant kinetics
- Most metabolised through cytochrome P450 system
- Concentration-related CNS toxicity can be partly avoided by TDM
- However severe skin rashes, liver and marrow toxicity cannot be predicted or avoided
- With phenytoin small dose increases can produce disproportionate rises in blood levels and toxicity
- Sometimes free (unbound) concentrations need to be measured - eg hypoalbuminaemia, pregnancy

Digoxin

- Has variable bioavailability
- Has variable clearance (by kidney) - remember the elderly
- Drug interactions are fairly common
- Relationship between concentration and effect is not constant - concentrations soon after dosing are difficult to interpret. Range is approx 1 to 2 nmol/L
- Patients may become more ‘sensitive’ to a given concentration - eg hypokalalaemia, hypothyroidism
- In atrial fibrillation titrate against the ventricular rate
- Concentrations should be measure at least 6-8 hours after the last dose

i) Pharmacokinetic Parameters and TDM Information

Parameter	Value
Elimination half-life '$t_{1/2}$' (hr)	36 hr (adults) 18-37 hr (children)
Total body clearance (ml/min/kg) 'TBC'	2.7
Volume of distribution * 'V'	6-7 L/kg (total body weight)
Plasma protein binding	20-30%
Therapeutic range	0.9-2 ng/ml for a-fib (0.5-1.2 for CHF)
Time to steady state** concentration	6-10 days
Loading dose***	Two 0.5mg oral tablet doses or Two 0.375mg IV doses, Separated by 6 hours (pts. with creatinine clearance > 20ml/min) 0.2 mg/day (creatinine clearance > 20ml/min)
Maintenance dose#	0.125 mg/day (creatinine clearance <20ml/min or body weight<40 kg)
Clinically important metabolite	Bis and mono-digitoxosides As cardioactive as digoxin

Cyclosporin

- Used as immunosuppressant in transplant rejection
- Low therapeutic index and toxicity (kidney) is severe
- Interactions are common - eg calcium channel antagonists
- Plasma range 50-300 mg/L

Theophylline

- Declining use in asthma
- Very narrow therapeutic index: 55 - 110 umol/L (should be lower)
- At the high end toxicity is common
- Toxicity is severe - GI, neuro, cardiac
- Interactions are common - erythromycin, cyclosporin, cimetidine, smoking

Gentamicin

- Practice is changing - trend to once/daily dosing
- Toxicity relates to trough concentrations, particularly with prolonged therapy
- Desirable range:
  - peak 6 - 10 mg/L
  - trough 1-2 mg/L

Fig. 19.1: Example of a TDM request form

Patient's name: _____ Date: _____

Age: _____ Sex: M F Wt: _____ kg

Hospital : _____ Ward or clinic: _____

PLEASE INDICATE WHEN RESULT IS NEEDED

Within 24 Hrs Within 2–4 Hrs Stat

REASON FOR REQUEST

Suspected toxicity Possible drug interaction
Therapeutic confirmation Lack of therapeutic response

Other (please specify) _____

Co-morbidities or other clinical comments

Name of drug to be assayed _____

Dose _____ Frequency _____ Dosage form _____

Route of administration (please circle): IV IM PO SC

Duration of therapy _____

Time and date of last dose _____

Time and date when sample was drawn _____

Doctor's signature _____

Contact details for urgent results _____