

THERAPEUTIC DRUG MONITORING

INTRODUCTION

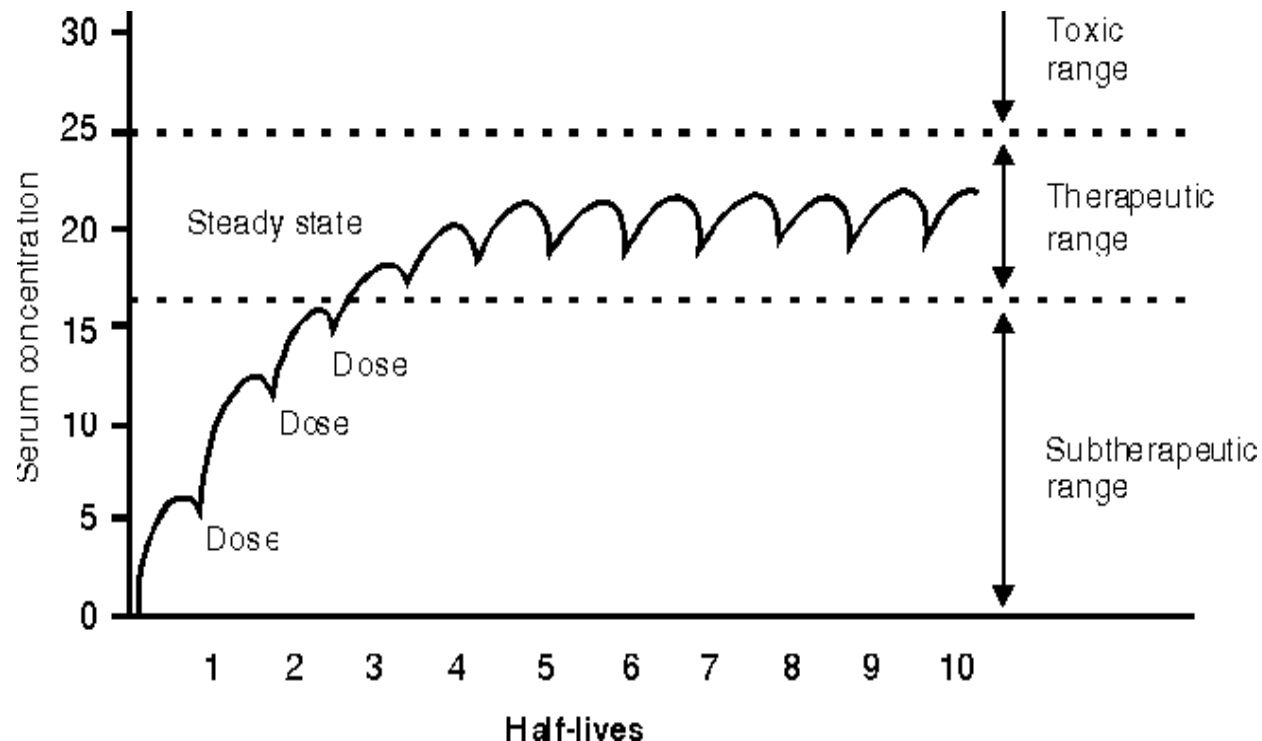
- Therapeutic drug monitoring (TDM) is generally defined as the *clinical laboratory measurement of a chemical parameter that, with appropriate medical interpretation, will directly influence drug prescribing procedures.*
- It involves the *use of drug concentration measurements in body fluids as an aid to the management of drug therapy for the cure, alleviation or prevention of disease.*
- TDM enables the assessment of the *efficacy and safety* of a particular medication in a variety of clinical settings.
- The goal of this process is to *individualize therapeutic regimens for optimal patient benefit.*

CONCEPT OF THERAPEUTIC DRUG MONITORING (TDM)

- TDM is based on the principle that *for some drugs there is a close relationship between the plasma level of the drug and its clinical effect.*
- If such a relationship does *not* exist *TDM is of little value.*
- The clinical value of plasma level monitoring depends on how precisely the treatment outcome can be defined.
- When a precise therapeutic end point is difficult to define, monitoring of drug levels may be of considerable therapeutic assistance.

THERAPEUTIC RANGE/ THERAPEUTIC WINDOW

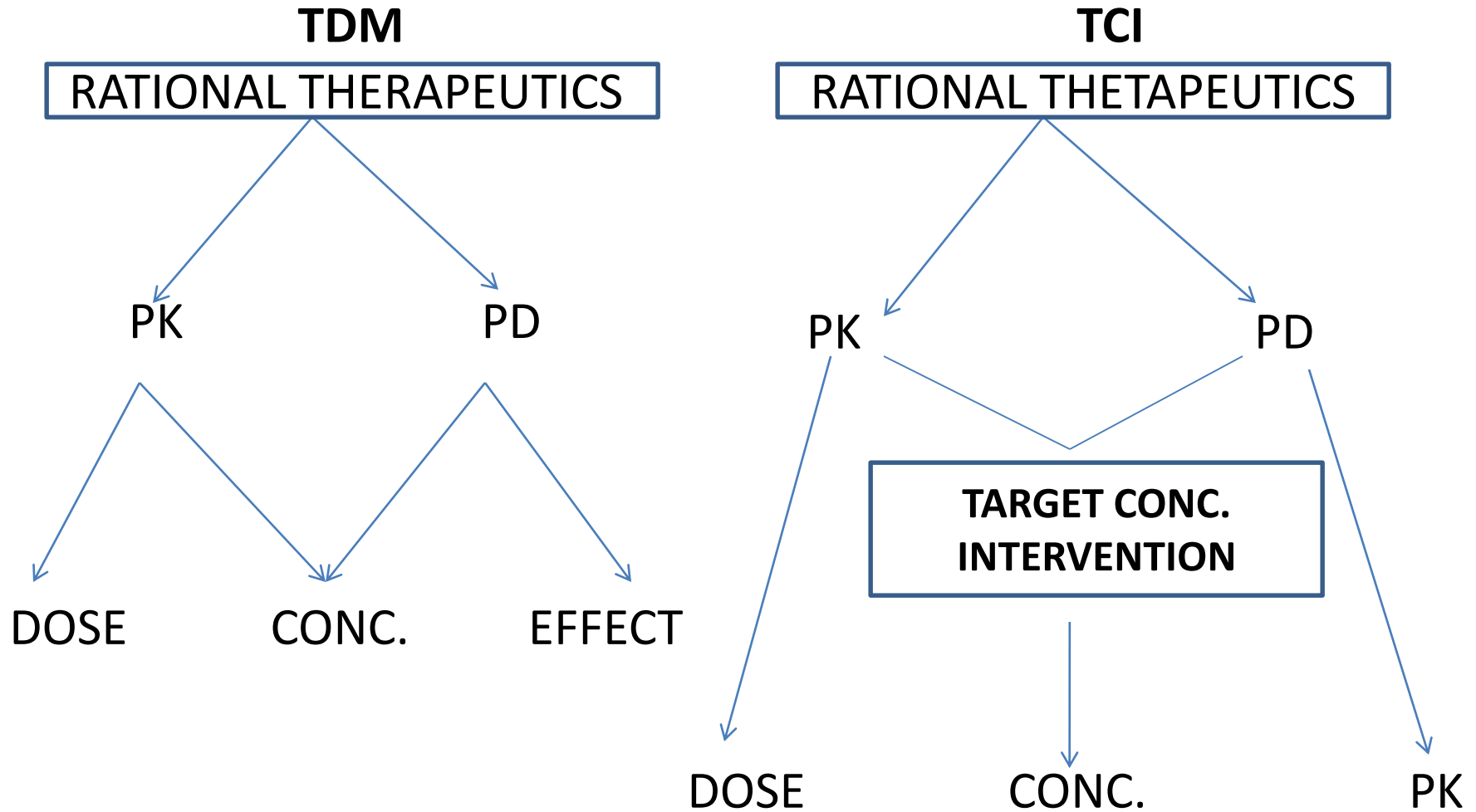
- The therapeutic range/ therapeutic window is the concentration range of drug in plasma where the drug has been shown to be efficacious without causing toxic effects in most people.



TARGET CONCENTRATION AND THERAPEUTIC RANGE

- The therapeutic range concept suffers from two strategic deficiencies.
 - First the idea of a range introduces uncertainty into exactly how to prescribe the desired dose.
 - The second deficiency is the implicit assumption that all concentrations within the range are equally desirable.
- On the other hand, the target concentration is directly linked to a specific dose for an individual - not a range of doses.
- Selection of a target concentration requires an understanding of the concentration-effect relationship, i.e. pharmacodynamics, for both desired and undesired effects. The target concentration is chosen to optimize the balance between these effects.

ALGORITHM TO SHOW DIFFERENCE BETWEEN TDM AND TARGET CONCENTRATION INTERVENTION(TCI)



STEPS INVOLVED IN TARGET CONCENTRATION STRATEGY

- 1) Select a target concentration
- 2) Predict clearance and volume of distribution values for the patient based on population pharmacokinetic parameters and observable individual characteristics (weight, renal function)
- 3) Calculate the loading dose and maintenance dose rate to achieve the target concentration
- 4) Administer the doses and measure drug concentrations
- 5) Use the measured concentrations to predict individualized values of clearance and volume of distribution for the patient
- 6) If appropriate, revise the target concentration for the individual based on clinical assessment
- 7) Revert to step 3.

TDM OF ESTABLISHED DRUGS

- 1. Cardio active drugs** : Amiodarone, digoxin, digitoxin, disopyramide
lignocaine, procainamide, propranolol and quinidine
- 2. Antibiotics** : Gentamicin, amikacin and tobramycin
- 3. Antidepressants** : Lithium and tricyclic antidepressants
- 4. Antiepileptic drugs** : Phenytoin, phenobarbitone, benzodiazepines,
carbamazepine, valproic acid and ethosuximide
- 5. Bronchodilators** : Theophylline
- 6. Cancer chemotherapy** : Methotrexate
- 7. Immunosuppressives** : Cyclosporine, Tacrolimus

TDM -INDICATIONS

1. Drugs for which relationship between dose and plasma concentration is unpredictable, e.g **Phenytoin**
2. Drugs with a **narrow therapeutic window**:- will allow dosage alterations to produce **optimal therapeutic** effect or to avoid **toxic effects**. **Ex:** Lithium, phenytoin, and digoxin
3. Drugs with steep dose response curve: e.g. **theophylline**.
4. Drugs for which there is difficulty in measuring or interpreting the clinical evidence of therapeutic or toxic effects:- Nausea & vomiting occur in both **digitalis toxicity** & **congestive heart failure**.
5. Drug with saturable metabolism: Phenytoin
6. Drug with poorly defined end point or difficult to clinically predict the response. Example: immunosuppressant drugs

TDM -INDICATIONS

7. Renal disease: Alter the relationship between dose & the plasma concentration. Important in case of digoxin, lithium & aminoglycoside antibiotics.
8. Drug interactions: When another drug alters the relationship between dose & plasma concentration e.g. plasma concentration of **lithium** is increased by **thiazide**.
9. Drug with large individual variability at steady state PDC in any given dose
10. For diagnosis of suspected toxicity & determining drug abuse
11. To evaluate compliance of patient
12. Guiding withdrawal of therapy: Antiepileptics, Cyclosporine.

DRUGS THAT ARE NOT SUITABLE FOR TDM

- 1) Drugs having wide therapeutic index
- 2) Toxicity is not a realistic concern (**Penicillin**)
- 3) Effects can be measured using functional laboratory tests (**Anticoagulants**)
- 4) Plasma concentration not predictably related to effects (**Anticoagulants**)
- 5) Effect of the relationship remains undefined (**Antidepressants**)
- 6) Hit and run drugs: **Omeprazole, MAO inhibitors**

BASIC PRINCIPLES OF THERAPEUTIC DRUG MONITORING

- The following are important considerations to ensure an optimum TDM service in any setting:
 - (1) Measurement of patient's serum or plasma drug concentration taken at appropriate time after drug administration
 - (2) Knowledge of pharmacological and pharmacokinetic profiles of the administered drugs
 - (3) Knowledge of relevant patient's profile like demographic data, clinical status, laboratory and other clinical investigations, and
 - (4) Interpretation of SDC after taking into consideration all of the above information and individualizing drug regimen according to the clinical needs of the patient.

PROCESS OF TDM

- Development of plasma profile in each patient
 - 1) Administering a predetermined dose of drug
 - 2) Collection of blood samples
 - 3) Determination of blood samples
 - 4) Plasma profile and pharmacokinetic model development:
 - Clinical effect of drug
 - Development of dosage regimen
 - Diagnosis, dosage form selection, dosage regimen, initiation of therapy



EVALUATION OF CLINICAL RESPONSE

SAMPLES

- Sample selection must include an ***appropriate matrix***.
 - **Plasma or serum** is commonly used for drug assays.
 - **Whole blood**:- for Cyclosporine, tacrolimus, sirolimus, as there are large shifts of drug between red cells and plasma with storage and temperature change.
 - **Saliva**, which gives a measure of the unbound drug concentration, may be a useful alternative when blood samples are difficult to collect.
Ex: Phenytoin ,Lithium, Amitryptiline
- Before collecting the sample:
 - Establish that SDC is at steady-state
 - Ensure complete absorption and distribution

- Samples should be collected and centrifuged as soon as possible.
- ***Avoid serum-separator tubes*** because these may lower drug concentrations due to the adsorption of drug into the matrix.
- **Storage of samples:** ***Plastic cryovial type tubes*** are acceptable for most assays.
- **For CSA:** Whole blood to be collected in an ***EDTA tube***.
- Analytical methods may be affected by ***temperature*** and all ***variables should be standardized***.

GUIDELINES TO SPECIMEN COLLECTION

- Drawn blood, used for TDM, ***demonstrates a drug action in the body at any specific time.*** Therefore, blood testing is the procedure of choice when definite data are required.
- For adequate absorption and therapeutic levels to be accurate, it is important to allow for ***sufficient time to pass between*** the administration of the medication and the collection of the blood sample.
- Blood specimens for drug monitoring can be taken at two different times: during the drug's highest therapeutic concentration (***'peak' level***), or its lowest (***'trough' level***).
- Occasionally called residual levels, ***trough levels show sufficient therapeutic levels;*** whereas ***peak levels show toxicity.***
- Peak and trough levels should fall within the therapeutic range.

- Patients receiving a drug at a ***dosing interval longer than the half-life*** of the drug will demonstrate ***large fluctuations between peak and trough levels***.
- Plasma concentrations of drugs ***dosed at intervals shorter than their half-lives*** would show ***less fluctuation between peak and trough levels***.
- For ***chronically administered oral medications*** the ***peak levels usually occur 1-2 hours after the dose*** and the ***trough serum concentration shortly after the dose is administered***.
- Digoxin is one exception. The serum level to determine peak activity should be drawn after the serum digoxin has ***had time to equilibrate with the tissue i.e., 6-10 hours after the oral dose***.
- Drawing the trough level at the time the dose is given is usually sufficiently accurate.

- ***Intravenous medications*** should also be given time to equilibrate before the peak level is drawn. They should be ***sampled ½-1 hour after administration.***
- For example, the peak serum level of Gentamicin should be drawn ***thirty minutes after infusion of the drug ends and not immediately after the infusion.***
- ***Intramuscularly administered*** medications if injected in an area with good blood flow will achieve peak levels within a similar time frame as intravenous.
- Medications that are ***poorly soluble at body pH***, however, may ***precipitate at the site of injection*** and achieve very ***low and late peak serum levels.***

- The clinician should know what questions are to be answered by the sample being drawn as ***different questions may require different sampling times and possibly different numbers of samples.***
- For example the question of ***toxicity*** may be answered by only ***one stat sample*** whereas a ***determination of half-life*** will require at least ***two samples drawn at a more precise time*** after the drug is administered.
- For patients suspected of symptoms of ***drug toxicity***, the best time to draw the blood specimen is ***when the symptoms are occurring; i.e., immediately at the time of presentation.***

TIMING OF SAMPLE COLLECTION

- The best sampling time is in the *predose or trough phase*, when a drug is administered by multiple oral doses.
- Trough conc. are *commonly used* for many drugs.
- Peak conc. may be useful for some antibiotics: Aminoglycosides
- Correct sample timing should also take into account *absorption and distribution*, eg digoxin samples are collected after 6 hours of administration.

TIMING OF SAMPLE COLLECTION

- For ***short half-life drugs***, more than one sample (***three is ideal***) is the most useful for determining individual pharmacokinetic parameters. Alternatively, a peak (C_{MAX}) and a trough (C_{MIN}) can be collected to determine the bounds of high and low concentrations at steady-state.
- For ***long half-life drugs*** (digoxin, phenobarbital), ***a single sample during the dosing interval*** is sufficient. If one suspects altered clearance rates, more samples can be collected to assess half-life.
- For ***cyclosporine***, a single trough sample has been used for many years, but now recommendations are changing to a single two hour sample (C₂). ***For cyclosporine a “trough” usually refers to a 12 hour sample, even though this drug is used once a day, or once every other day in some patients.***

SAMPLE TIMING FOR SOME IMPORTANT DRUGS

- a) **Phenytoin:** Since phenytoin has a long half life a single daily dose may be employed and so the timing of concentration monitoring is not critical.
- b) **Carbamazepine:** Its half life may be as long as 48 h following a single dose. A trough concentration taken just after a dose together with a peak level 3 hours later is ideal.
- c) **Digoxin:** The measurement must be made atleast 6 hours after a dose to avoid inappropriate high levels.
- d) **Theophylline:** This drug has a narrow therapeutic index and timing of sampling is not critical if the patient is receiving one of the slow release formulations, wherein trough levels should be taken.
- e) **Lithium:** A 12 hr sample gives the most precise guide to dosage adjustment.
- f) **Gentamicin:** Pre dose peak; 0.5 hr after i.v. And 1 hr after i.m. administration.

SAMPLE CONCENTRATIONS

Lower than anticipated

- Patient non compliance
- Error in dosage regimen
- Rapid elimination
- Timing of sample
- Changing hepatic blood flow
- Poor bioavailability
- Reduced plasma binding

Higher than anticipated

- Error in dosage regimen
- Rapid bioavailability
- Slow elimination
- Increased plasma protein binding
- Decreased renal/hepatic function

INTERPRETIVE CRITERIA

- **Therapeutic ranges:** These are the recommendations derived by observing the *clinical responses* of a small group of patients taking the drug.
- The *lower limit* is set to provide ~50% of the *maximum therapeutic effect*, while the *upper limit* is defined by *toxicity*.
- Therapeutic ranges are *not absolutes* and hence *expert clinical interpretation* of the obtained value is necessary to derive meaning from the result.
- Data on *duration of drug therapy, dosage and time of the last dosage* is important.
- True TDM testing takes into consideration all the *factors that can affect results and interpretation*.

FACTORS THAT AFFECT RESULTS

- Pharmacokinetics
- Pharmacodynamics
- Dose
- Sampling time and type
- Testing methodology
- Genetic polymorphisms
- **Other variables:** Smoking, drug formulation and circadian effect, use of *Alternative system of medicine*.
{shankhapushpi vs phenytoin}
- Interaction with conventional drugs have been documented for *liquorice, ginseng, tannic acids, plantain, uzara root, hawthorn and kyushin*.

MAJOR SOURCES OF PHARMACOKINETIC VARIABILITY

- Patient Compliance – lack of
- Age – neonates, children, elderly
- Physiology – gender, pregnancy
- Disease – hepatic, renal, cardiovascular, respiratory
- Drug-to-drug interactions
- Environmental influences

- **Sampling time** is critical, since the **drug concentration varies over the entire dosing interval** and with the duration of dosing in relation to achieving a steady state.
- **Trough values** are the **least variable** concentrations and are most often **used to establish therapeutic ranges**. Drugs with **short half-lives** require trough concentration monitoring. Drugs with a **long half-life** can be monitored at any point in the dosage interval.
- Additional consideration should be given to the **type of sample tested** as some anticoagulants may interfere with results for certain drugs (**lithium: heparin affects lithium results**), while some **gel separators** interfere with the results of other drugs.
- The **sensitivity and specificity** of the testing methodology must also be considered.

FACTORS THAT AFFECT INTERPRETATION

- These vary from drug to drug.

Protein Binding

- TDM assays typically require serum or plasma and usually measure ***both the bound and unbound drug***, even though it is the unbound drug that reacts with the receptor to produce a response.
- This is seldom an issue – unless the ***patient's binding capacity is altered*** due to ***disease-state, drug interaction, or non-linear binding***. In such cases, the effect of the protein binding needs to be taken into consideration when interpreting results.

Active Metabolites

- Many therapeutic drug metabolites, though not measured, ***contribute to a drug's therapeutic response***. For example, primidone treatment is monitored by measuring phenobarbitone, an active metabolite, but primidone itself and other metabolites are also active.

Steady State

- Unless a ***loading dose or i.v. infusion*** is used initially, steady state must be reached before meaningful TDM is possible for those drugs that are given long-term.

Turnaround Time

- Turnaround time is important to ensure that the physician has ***time to evaluate the result before the patient is scheduled to receive the next dose.***
- For most drugs this is not an issue, as assays for the most commonly tested analytes are available on several fully automated analyzers.
- However, for ***drugs without commercially available assays***, highly specialized chromatographic and ultra-filtration assays are used. These methods require specially trained staff and are most often performed in a limited number of sites. Therefore, ***results tend to take longer to receive.***

PHARMACOKINETIC PARAMETERS

- Five pharmacokinetic parameters that are important in therapeutic drug monitoring include:
 - i. **Bioavailability.**
 - ii. **Volume of distribution and distribution phases.**
 - iii. **Clearance**
 - iv. **Half-life**
 - v. **Protein binding of drugs.**

TDM OF CYCLOSPORINE

- Monitoring should take into account:
 - 1) the blood level of cyclosporine and the therapeutic interval (different for renal, liver and heart transplantation)
 - 2) the correlation that exists between therapeutic interval and acute graft rejection and nephrotoxicity.
- Frequency of cyclosporine blood levels determination should be at ***2-3 days (in the first 4 weeks post-transplant), then monthly after 3 months.***
- Because cyclosporine binds significantly to red blood cells, **whole blood** is a better biological matrix for assessing cyclosporine concentration than plasma.

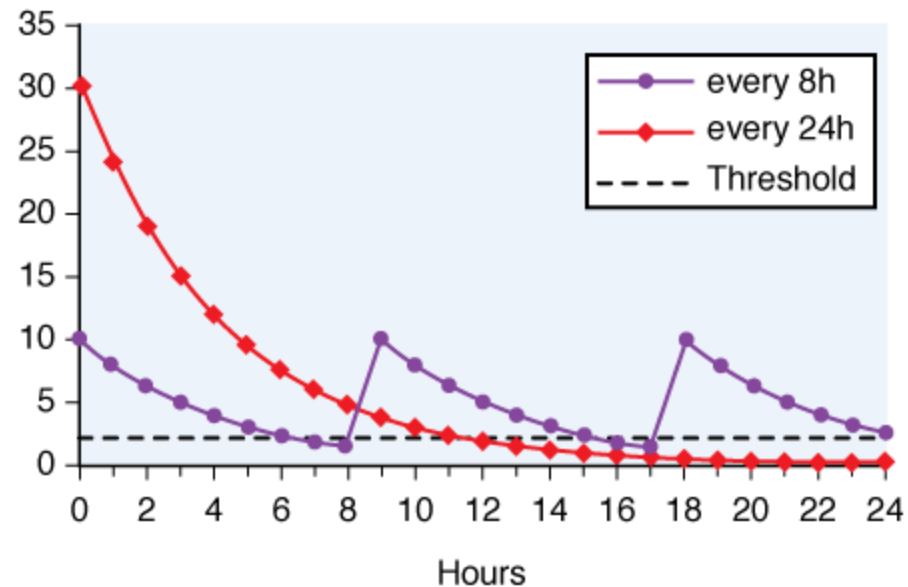
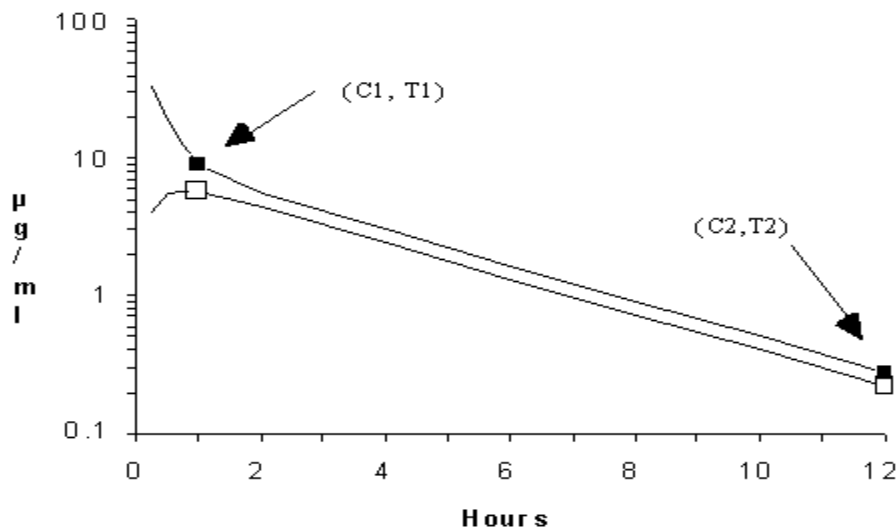
- The purpose of monitoring is to ***prevent rejection and improve tolerance (avoidance of nephrotoxicity and too high immunosuppression)***.
- C_{trough} residual concentration (C_0 , pre-dose concentration) is ***directly correlated with nephrotoxicity***, but it is ***not a useful marker for prediction of acute rejection***.
- Instead, ***both nephrotoxicity and acute rejection are better correlated with the area under the concentration-time curve measured between 0 - 4 h or 0-12 h (AUC₀₋₄, AUC₀₋₁₂)***.
- ***These values can be better estimated using the value of C_2 (blood level 2 h post-dose) than the residual concentration (C_0)***. {greatest variability occurred in the absorption phase in the initial 4-6hr after the CsA dose}
- ***C_2 concentration can be used as a surrogate index of CsA absorption and exposure***.

No. crt.	Transplant type	Target values (whole blood)		Observations
		C ₀ (ng/mL)	C ₂ (mg/L)	
1	Renal	200-400	1.4-2	15 days post-transplant
		125-275	1.2-1.8	2-3 months post-transplant (good renal function)
		100-125		2-3 months post-transplant (poor renal function)
		100-150	0.7 -1	6 months – 1 year post-transplant
		75-150		> 1 year post-trasplant
2	Hepathic	250-350	0.8-1.2	First 6 months
		100-200	0.6 -1*	6 months – 1 year post-transplant
3	Cardiac	250-350		initially
		100-200	0.3-0.6	6 months – 1 year post-trasplant

TDM: AMINOGLYCOSIDES

Need for monitoring:

- Bactericidal activity linked to peak concentration
 - Desired profile: high peak
- Toxicity (ototoxicity, nephrotoxicity) related to total drug exposure
 - Desired profile: low trough (no accumulation)
- Traditional monitoring: peak and trough concentration
- **Targets for IV GENTAMICIN:** Peak 30-60 min post-dose = 5-10 mg/L
Trough before next dose < 2 mg/L



TDM: PHENYTOIN

Therapeutic range - 10-20 μ g/mL

Time to steady state: 7-10 days.

Need for monitoring:

- Narrow therapeutic window
- Highly protein-bound; drug-drug interactions, drug-disease interactions
- Non-linear pharmacokinetics even within the therapeutic range
- Inter-individual variability in enzyme saturation

Approximately 90% of phenytoin is bound to albumin. Thus, phenytoin levels must be corrected according to albumin levels.

- Corrected phenytoin (mg/L) =
$$\frac{\text{Observed phenytoin (mg/L)}}{(0.2 \times \text{albumin [g/dL]}) + 0.1}$$

Phenytoin levels are generally monitored at 3 to 12 months intervals

Common dose-related side effects

Central nervous system effects: somnolence, fatigue, dizziness, confusion, visual disturbances, nystagmus, ataxia

Gastrointestinal side effects: nausea, vomiting, anorexia

> 20 mg/L: far lateral nystagmus

> 30 mg/L: 45° lateral gaze nystagmus and ataxia

> 40 mg/L: decreased mentation

> 100 mg/L: death

WHEN SHOULD PHENYTOIN LEVELS BE TAKEN?

Newly Started Patient on Phenytoin	Suspected Non-compliance/ Breakthrough Seizures	After Dose Adjustment	Suspected Phenytoin Toxicity
Based on ROA of loading dose IV: one hour after the dose ORAL: 24Nhrs after the last dose	Levels can be drawn at the point of admission, regardless of the patient's normal dosing time.	Within six to seven days; trough level or at least eight hours after the last dose	Immediately; second phenytoin level may be useful to guide when to restart phenytoin. The lapse time in rechecking the phenytoin level should be determined by how high the first toxic level was, as phenytoin clearance dramatically slows with very toxic concentrations.

TDM: DIGOXIN

- **Therapeutic range** 1-2ng/L (taken >6h post-dosing; 1ng/L=1.3nmol/L) for inotropic effect not AF.
- **Steady state:** 3-5 half-lives (= 5-7 days normal t_{1/2}; 1-3 weeks renal dysfunction)
- **Toxicity** - may be nonspecific eg nausea, vomiting, abdominal pain & confusion, bradycardia (AV junctional escape rhythms) and visual disturbance.
- **PK problems** - 10% population have enteric bacterium (E. lentum) that can metabolize digoxin. Large volume of distribution (\approx 5L/kg lean BW) and predominantly excreted unchanged in the urine with $CL_{\infty} \propto GFR$.
- Large of number of interactions -

	Mechanism	Condition/Drug(s)
PK	↑ Vd and CL	Thyrotoxicosis/T4
	↓ Vd and/or CL	Verapamil, amiodarone, propafenone
	↑ absorption	Erythromycin, omeprazole
	↓ absorption	Exchange resins, kaolin
	↓ GFR	Any cause of renal impairment/Cyclosporine
PD	increase block of the Na pump	Hypokalaemia/Kaluretic diuretics

TDM: THEOPHYLLINE

- **Therapeutic range** - 5-20 μ g/ml
- **Time to steady state:** 36 hours (average).
- **Toxicity** - manifest as tachyarrhythmias, vomiting & convulsions.

PK problems - Bioavailability varies widely between preparations. 90% eliminated by the liver & 10% unchanged in the urine (reversed ratio in neonates) i.e. No adjustment for renal failure required but **↓ dose in presence of impaired hepatocellular function.**

Whenever possible establish drug level before administering IV and **if in doubt do not give bolus loading dose.**

Drawing levels:

- a] ***Oral solution or immediate-release tablet:*** 1-2 hours after administration.
- b] ***Extended-release tablet:*** 4-12 hours after administration.
- c] ***Injection:*** 30 minutes after completion of the intravenous loading dose; a second measurement should be obtained after one expected half-life- **4 hours in children age 1 to 9 years and 8 hours in nonsmoking adults.**

TECHNIQUES FOR MEASUREMENT OF TDM

- **HPLC: High Pressure Liquid Chromatography:** The separation of a substance depends on the relative distribution of mixture constituents between two phases, a mobile phase (carrying the mixture) and a stationary phase.
- **LC/MS: Liquid Chromatography Mass Spectrometry:** All chromatography-based techniques work on the principle that different substances are absorbed differently in solution. Two “phases” or materials are used to separate the components of a solution. The mobile phase carries the sample along the stationary or solid phase, which separates out the components in the sample.
- **GC/MS: Gas chromatography** is a separation method using very high temperatures to cause sample vaporization. In **mass spectrophotometry** the vaporized fractions are passed through an electrical field. The molecules can be separated on the basis of molecular weight. The pattern of separation is unique to each drug and therefore establishes a “fingerprint” for identification. GC/MS is the gold standard method for the identification of drugs of abuse.

- **EIA: Enzyme immunoassay.** EIA uses a non-radioactive enzyme label. Most of the drug testing today is performed using homogeneous EIA techniques. This refers to the fact that the assays are performed in a single step, i.e. only one antibody is used in the procedure. Therefore, the turnaround time for testing is reduced.
- **RIA:** Use radioactivity to detect the presence of the analyte. In RIA, the sample is incubated with an antibody and a radio-labeled drug. The amount of radioactivity measured is compared to the radioactivity present in known standards which are included in each run. Results are quantitative.
- **PETINIA:** An immunoturbidimetric method; **Particle Enhanced Turbidimetric Inhibition Immunoassay.** This method uses the creation of light scattering particles to measure drug levels.
- **EMIT: Enzyme Multiplied Immunoassay Technique;** based on competition for the target analyte antibody binding sites.

- **FPIA: Fluorescence Polarization Immunoassay.** This method uses a fluorescent molecule as the label instead of an enzyme, making it more sensitive.
- **Chemiluminescence:** This is a chemical reaction that emits energy in the form of light. When used in combination with immunoassay technology, the light produced by the reaction indicates the amount of analyte in a sample. The most common chemiluminescent assay methods are either enzyme-amplified or direct chemiluminescent measurements.
- **ACMIA: Affinity Chrome-Mediated Immunoassay.** ACMIA is a technique to measure drug concentrations in which free and drug-bound antibody enzyme conjugates are separated using magnetic (chrome) particles.
- **CEDIA: Cloned Enzyme Donor Immunoassay.** CEDIA employs a recombinant DNA technology.

CLINICAL SIGNIFICANCE OF TDM

1. Maximizes efficacy
2. Avoids toxicity
3. Identifies therapeutic failure
 - Non compliance, subtherapeutic dose
4. Facilitates adjustment of dosage
 - New dose = Old dose X Desired C_{ss} /Old C_{ss}
5. Facilitates the therapeutic effect of drug by achieving target drug concentration
6. Identify poisoning, drug toxicity and drug abuse

REQUEST FORM OF TDM

Patient Name..... Date..... HN.....

Age..... Sex..... Wt..... Ht.....

Ward..... Ordered by..... Phone No.....

DRUG LEVEL REQUESTED.....

REASON FOR REQUEST :

- Suspected toxicity Compliance
 Therapeutic confirmation Absence of therapeutic response

Please indicate when level is needed :

- within 24 h within 1-2 h stat others.....

TIME AND DATE OF LAST DOSE :

Date..... Route : IV, IM, SC, PO, Others.....

Time..... Dose..... Freq.....

THIS DRUG LEVEL IS FOR :

SAMPLING TIME :

Trough or predose level Date..... Time.....

Peak level Date..... Time.....

DOES THE PATIENT HAVE ORGAN-SYSTEM DAMAGE ?

- Renal Hepatic Cardiac GI Endocrine Others.....

OTHER DRUG(S) PATIENT IS TAKING :.....

DRUG LEVEL & USUAL THERAPEUTIC RANGE.....

INTERPRETATION.....

.....

Date..... Technologist..... Time.....

PRACTICAL ISSUES IN THERAPEUTIC DRUG MONITORING

- Ideally, a quality drug assay should be performed within a time frame that is *clinically useful*.
- Once the decision to monitor the concentration of a therapeutic drug has been made, it is important that a *biological sample is collected to provide a clinically meaningful measurement*.
- An appropriate pharmacokinetic evaluation requires the acquisition of *properly timed blood specimens*.
- *Absorption is variable after oral administration, and blood samples should be collected in the elimination phase rather than in the absorption or distribution phases.*

- Although plasma concentrations for many drugs peak 1 to 2 h after an oral dose is administered, factors such as slow absorption can significantly delay the time at which peak plasma concentrations are attained.
- Therefore, with few exceptions, ***plasma samples should be drawn at trough, as*** trough levels are ***less likely to be influenced by absorption and distribution problems.***
- Concentrations measured at these time points can be compared with published therapeutic ranges, that relate trough drug concentrations measured at steady state to pharmacodynamic responses.
- If a given dose of a drug produced the ***same plasma concentration*** in all patients, there would be ***no need to measure the plasma concentration of the drug.***

- If active metabolites are produced, ***both the parent drug and the metabolites must be measured*** to provide a comprehensive picture of the relationship between the total plasma concentration of the active compounds and the clinical effect.
- This is usually not possible in routine monitoring, which ***limits*** the usefulness of plasma concentration measurements of drugs that produce active metabolites.
- The assay results should be available quickly, preferably ***within 24 h of receiving the sample.***
- The most important consideration in interpreting the plasma drug concentration is ***tailoring the treatment to the patient's physiological needs.***
- Hence, the clinician should take into account not only the concentration but also other ***clinical features that may affect the relationship between concentration and clinical effects.***

FREE DRUG MONITORING

- Development of *new filtration devices (equilibrium dialysis, ultrafiltration, ultracentrifugation)* has made it possible to measure free unbound drug levels in serum.
- The advantages are that the free concentrations is *independent of changes in plasma binding* and is the *pharmacologically active concentration*.
- The disadvantages are that it is *time consuming, expensive and therapeutic ranges do not yet exist for many drugs*.

DRUG CONCENTRATION IN OTHER FLUIDS OF BODY BE MEASURED

- Urine: Benzodiazepines
- Sweat: Cocaine & Heroin
- Saliva: Marijuana, Cocaine, Alcohol
- Breath: Alcohol

USE OF SALIVA IN DRUG MONITORING

- The concentration of a drug in saliva is *proportional* to the concentration of the unbound drug in plasma.
- The practice of measuring drugs in saliva is *appealing* because it is *non invasive*.
- However it has its *limitations* viz.,
 - Some substances such as lithium are actively secreted into the saliva rather than by passive process.
 - Drug binding to salivary proteins may produce discrepancies in plasma/salivary ratios, e.g. phenytoin.
 - Drugs may also bind to oral cell debris, e.g. propranolol
 - Salivary flow may be reduced in patients taking anti cholinergic drugs.
 - Preparations used to stimulate salivary flow might interfere with drug estimation e.g. lemon flavored sweets interfere with amitriptyline estimations.

COST EFFECTIVENESS

- The measurement of drug levels in body fluids must be cost effective.
- The cost of performing an individual test is determined by the ***summing equipment, personnel, supply and overhead expenditure for a given period of time*** and dividing that amount by the ***number of assays performed in the same time interval***.
- The fee charges is then determined by the ***test's cost plus desired profit***. The foregoing calculations may produce an ***unreasonably expensive fee***.
- However, use of clinical pharmacokinetics by therapeutic drug monitoring service offers substantial benefits like ***fewer adverse reactions, shorter intensive care unit stay and shorter overall hospital stay***.