

A REVIEW ARTICLE ON THERAPEUTIC DRUG MONITORING

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ABSTRACT

DRUG MONITORING (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. 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. 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.

1. INTRODUCTION

Therapeutic drug monitoring (TDM) was started as an attempt to protect patients against drug toxicity. Digoxin assays were the first to emerge in the market and used by the laboratories.¹ After five decades, TDM has evolved as a field where laboratory and clinical specialists join on the common purpose of personalizing the dosage of therapeutic agents.^{2,3} Anti-epileptic drugs (AEDs) are perfectly suitable for TDM due to their narrow marked inter-individual pharmacokinetic variability. Till date, there are no clear definitions that can guide the clinician to decide on a specific AED with a specific dosage on an individual patient.

When initiating a medical therapy, the clinician is almost blind to predict if the patient will respond well to the drug of choice or experience unwanted drug effects. At this point TDM aims to contribute to the decision making. The medical staff is responsible against the patient to manage the therapy with the most appropriate dosage of drug. Digoxin is used by the elderly, a population with physiologic multiorgan malfunctions that label every patient with a potential of unexpected response to medication. In case of digoxin, the major concern has been drug toxicity. When dealing with AED, TDM requires more than simply measuring patients blood drug concentrations and compare them to a target range, but to keep the patient safe from convulsions as long as possible or ideally eliminate the disease with the minimal dosage of the drug used.

It is called “individualization” of drug dosage.⁴ In TDM practice, the clinician tries to maintain serum drug concentrations within a pre-defined therapeutic range, which defines the highest probability that the patient will benefit from the drug and be safe from side effects. However, it should not be forgotten that these ranges are statistical findings and there will always be patients who recover with sub-therapeutic dosages and who will suffer side effects or even toxicity within therapeutic levels.

There is a debate on the efficiency of TDM in the literature.^{5,6} The utility of TDM has not been clearly established. TDM is costly and pressure continues within the healthcare system of many countries to provide services at the lowest possible cost. Rational utilisation of TDM is an exact partner of drug dosage individualization. When used appropriately, it may improve patient management by maximising disease control and minimising the risk of adverse drug reactions; finally have a cost-saving effect.³ To optimize the use of TDM in laboratory, it is essential for the TDM performers to share experiences.

The present study shares our experience with TDM for phenytoin, valproic acid, carbamazepine and digoxin in a period of 10 months.

MATERIAL AND METHODS The study was conducted in a community hospital which serves as a teaching hospital and also as a tertiary care referral centre with 950 bed capacity. The central laboratory facilitates the needs of the entire hospital including smaller medical units. TDM was initially run by the Clinical Pharmacology Department between 2010 and 2011.

After January 2011 TDM unit was moved to the Central Laboratory under the control of Clinical Biochemistry. TDM test panel in our hospital currently includes phenytoin, carbamazepine, valproic acid and digoxin. This is a

retrospective analysis of the existing electronic database. TDM tests were identified through a code search between 1/3/2013 and 31/12/2013. Database search was conducted to collect the information such as name, age and gender of the patients, the unit requesting the test. After the test was requested by the clinician, the patients were sent to the sample stations where the blood was collected by direct puncture to a vein. Blood was drawn into a 4 mL serum tube with a gel separator. Serum was separated by centrifuging the blood at 3000 rpm for 10 minutes.

DISCUSSION Situations that may be appropriate for TDM include dosage adjustment, confirmation of suspected toxicity, identification of non-compliance, management of drug interactions and specific clinical conditions like in the cases of uremic patients, patients with liver disease, pediatric and geriatric patients, critically ill patients and pregnant.2-4 High percentage of supra-therapeutic digoxin test results emphasizes the use of TDM for this drug as confirmation of suspected toxicity or overdose.

In general, drug overdose is evidenced by patients medical history and clinical findings. However, in some cases of digoxin overdose, the findings may pose a dilemma that the clinician may ask for TDM. Considering the second largest group of requests from Intensive Care Unit, it seems quite clear that clinicians were uncomfortable with critically patients using digoxin.

The digoxin requests from Nephrology Department were more than the requests from Cardiology Department TDM results for appropriateness of test requests.¹¹ Only 26% of the tests were with a request form, so the remaining 74% was excluded in the study. The authors reported an extremely high percentage of appropriate ness (77%) in their study. Schoenenberger et al. found the percentage of appropriateness as 27 % in their study.¹³ Related to our previous assumption, we think that the excluded majority was a question mark for the reliability of the former study results.

2. 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

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 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 immuno-suppression) The residual concentration (C0, 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, AUC 0-12) These values can be better estimated using the value of C2 (blood level 2 h post-dose) than the residual concentration (C0). {greatest variability occurred in the absorption phase in the initial 4-6hr after the CsA dose} C2 concentration can be used as a surrogate index of CsA absorption and exposure.

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) = Observed phenytoin (mg/L) (0.2 x albumin [g/dL]) + 0.1 Phenyltoin levels are generally monitored at 3 to 12 months intervals

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

The 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 t1/2; 1-3 weeks renal dysfunction)
- Toxicity - may be nonspecific eg nausea, vomiting, abdominal pain & GFR Any cause of renal impairment/Cyclosporine PD increase block diuretics of the Na pump □ absorption Exchange resins, kaolin □ absorption Erythromycin, omeprazole □ Vd and/or CL Verapamil, amiodarone, propafenone □ Vd and CL Thyrotoxicosis/T4 □ GFR.
- Large of number of interactions - Mechanism Condition/Drug(s) PK □ 5L/kg lean BW) and predominantly excreted unchanged in the urine with CL □ 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

TDM: THEOPHYLLINE

- Therapeutic g/ml • Time to steady state: 36 hours (average).
- Toxicity - manifest as vomiting □ range - 5-20 & convulsions. PK problems - Bioavailability varies widely between preparations. 90% eliminated by the liver & 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.

3. 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 spectrometry 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

- Maximizes efficacy
- Avoids toxicity
- Identifies therapeutic failure – Non compliance, subtherapeutic dose
- Facilitates adjustment of dosage New dose = Old dose X Desired Css/Old Css
- Facilitates the therapeutic effect of drug by achieving target drug concentration
- Identify poisoning, drug toxicity and drug abuse

4. 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. 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. 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.

TDM: Clinical Interpretation For therapeutic drug monitoring the information required to allow interpretation of the result should include:

- Patient -Age, weight, sex, height, smoker status
- Clinical – clinical status renal -serum creatinine; cardiac -cardiac output; liver function
- Other drug therapy
- Relevant disease states
- time of the sample collection
- time of the last dose
- dosage regimen
- indication for drug monitoring e.g .lack of effect, routine monitoring, suspected toxicity

Serum conc. lower than anticipated Patient non compliance

- Error in dosage regimen
- Rapid elimination
- Timing of sample
- Steady state not reached
- Change in hepatic blood flow
- Induction of metabolizing enzymes
- Poor bioavailability
- Increased plasma protein binding
- Enlarged apparent volume of distribution

Serum conc. higher than anticipated

- Error in dosage regimen
- Increased bioavailability (hepatic disease)

- Slow elimination
- Inhibition of metabolizing enzymes
- Decreased plasma protein binding
- Smaller apparent volume of distribution
- Decreased renal function (important in case of digoxin, lithium, aminoglycoside antibiotics)
- Decreased hepatic function (theophylline)

Serum concentration correct but patient does not respond to therapy

- Altered receptor sensitivity (tolerance)
- Drug interaction at receptor site Dose adjustment
- If these factors can be eliminated, a dosage adjustment is required.
- For drugs with linear kinetics the following formulae may be used:
- New dose = Old dose X Desired drug concentration Old drug concentration

Clinical interpretation of results Clinical conditions requiring TDM Collection of biological sample Transfer to laboratory and estimation of drug concentration by suitable method Interpretation of TDM results with reference to clinical conditions Inadequate/Lack of Clinical response Satisfactory Clinical response/Toxicity Below TR Within TR Above TR Increase dose if required Change or re consider drug therapy If required a small change in dose should be considered Below TR Within TR Above TR Other possible reasons for signs of toxicity should be considered. Laboratory errors should be checked Other possible reasons for signs of toxicity should be considered. Lower dose can be given if result indicates the relief of disease Discontinue the therapy and restart with a low dose / alternate drug

TDM: Common drugs

- Cardio active drugs : – amiodarone, digoxin, digitoxin, disopyramide, lignocaine, procainamide, propranolol and quinidine
- Antibiotics : – gentamycin, amikacin and tobramycin
- Antidepressants – lithium and tricyclic antidepressants
- Antiepileptic drugs : – Phenytoin, phenobarbitone, benzodiazepines, carbamazepine, Valproic acid and ethosuximide
- Bronchodilators : – theophylline
- Cancer chemotherapy : – Methotrexate
- Immunosuppressives : – Cyclosporine

Drugs commonly monitored

- Anticonvulsants : – Managing non responders to a standard dose of a drug – Differentiate between non compliance, need for higher dose and true drug resistance requiring change or addition of another drug. – Situations like suspected drug toxicity, dose adjustments during pregnancy and lactation. – Target concentration selected which will lead to optimum seizure control. – Therapeutic range : Phenytoin – 10-20 ug/ml Valproic acid – 50-100 ug/ml
- Phenytoin & Sod. valproate – Sampling time: Immediately before next dose (trough level); Peak levels for confirming toxicity. Levels should be taken : Phenytoin 3-4 hours post dose; Valproate 1-3 hours post dose
- Range : Phenytoin 7-17 mg/L; Valproate: 40-120 mg/L
- Lithium : – Excreted unchanged by kidney, toxic conc. can cause, damage to renal and nervous system. – Sampling time: 12 hours after the preceding dose. – First TDM done within 48-72 hrs. – Subsequently done weekly for first month, then monthly for next 6 months to once every 4-6 months. – Therapeutic range is 0.5-0.8 mmol/l – Level above 2 mmol - severe toxicity.
- Antidepressants – plasma conc. at a given dose may vary in excess of 40 fold – Genetic polymorphism of metabolizing enzymes CYP 450
- Digoxin : – For confirmation of suspected toxicity, reasons of therapeutic failure, assessing factors like renal dysfunction and drug interactions. – Sample taken at least 8 hrs post dose to allow for redistribution. – Therapeutic range – 1.0 – 2.5 nmol/l
- Aminoglycosides : – Tissue accumulation related to nephrotoxicity and ototoxicity. – Peak and trough conc. measured in all pts. with renal failure and treatment exceeding 7 days . – Therapeutic range : Gentamicin 4-10 ug /ml

- Theophylline : – Narrow therapeutic index, variable metabolism – Sampling time: Immediately before next dose (trough level) – Done 72 hrs after any change in dose – Many drug interactions and interindividual variability – Therapeutic range : 5-20mg/l
- Cyclosporine : – Measured in whole bld – Therapeutic conc. - 80-200 nmol/l – Risk of transplant rejection in 1st 6 mon increases – when trough conc is <80nmol/l – Nephrotoxicity, hepatotoxicity & AE increases if conc 170-330nmol/l – Sampling time: just before next dose is due.
- Antitubercular drugs : – Slow responders, drug resistant cases – Drug interactions (esp. with concurrent HIV) and other associated disease states Antiretroviral drugs : – Useful in treatment naïve patients with wild type virus isolates – Athena study – better virologic outcomes and fewer treatment discontinuations with TDM as part of clinical care • Anticancer drugs : – Long term administration – Therapy essential for patient survival – Can produce serious side effects – E.g. – methotrexate, 5-fluorouracil, tacrolimus

TDM : Clinical Usefulness

- Maximizing efficacy – E.g. for Phenytoin in epilepsy, Theophylline in bronchial asthma
- Avoiding Toxicity – Overdose – Differentiating adverse effects from disease effects e.g. Digoxin toxicity & hypokalemia / ventricular arrhythmia – Altered pharmacokinetics (Hepatic / Renal failure)
- Identifying therapeutic failure – Non, compliance – Sub-therapeutic dose – Drug interactions – Decreased bioavailability / malabsorption
- Short hospital stay
- Better disease control
- Dose adjustment
- Dose guidelines
- Individualized dose requirement
- Avoidance of unnecessary medication

A retrospective survey carried out at the Massachusetts General Hospital showed that 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)

TDM: Problems

- Physicians sometimes do not understand the principles, benefits, and the limitations of TDM service
- Inappropriate sampling times
- Do not state the indication of TDM
- Insufficient patient's history and other necessary data

TDM: Limitations

- Scientific accuracy of drug assays
- Laboratory variability in reporting
- Validity of suggested target ranges.
- Limited accessibility and infrastructure facilities
- Lack of training and skills
- Cost involved

5. CONCLUSION:

The aim of therapeutic research is to find out an effective medication against the disease without any dangerous .

- The delicate problem is that very often the dose of drug confuses with toxicity.
- routinely monitor drug pharmacodynamics by Clinicians 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
- In these situations 'Therapeutic Drug Monitoring' becomes an essential part of A very useful tool that uses standard pharmacokinetic principles combined with the measurement of drug concentrations to monitor safety and efficacy of drugs.
- TDM is required for effective patient care management
- It leads to optimizing pharmacological therapy

6. REFERENCES

- [1] Touw DJ, Neef C, Thomson AH, Vinks AA. Cost-effectiveness of therapeutic drug monitoring: a systemic review. *Ther Drug Monit.* 2005;27:10–17.
- [2] Birkett DJ. Pharmacokinetics made easy: therapeutic drug monitoring. *Aust Prescr.* 1997;20:9–11.
- [3] Tange SM, Grey VL, Senecal PE. Therapeutic drug monitoring in pediatrics: a need for improvement. *J Clin Pharmacol.* 1994;34:200–214.
- [4] Reed MD, Blumer JL. Therapeutic drug monitoring in the pediatric intensive care unit. *Pediatr Clin North Am.* 1994;41:1227–1243.
- [5] Kearns GL, Moss MM, Clayton BD, Hewett DD. Pharmacokinetics and efficacy of digoxin specific Fab fragments in a child following massive digoxin overdose. *J Clin Pharmacol.* 1989;29:901–908.
- [6] Ohning BL. Neonatal pharmacodynamics-basic principles: I. drug delivery. *Neonatal Netw.* 1995;14:7–12.
- [7] Ohning BL. Neonatal pharmacodynamics-basic principles: II. drug action and elimination. *Neonatal Netw.* 1995;14:15–19.
- [8] Duhme DW, Greenblatt DJ, Koch-Weser J. Reduction of digoxin toxicity associated with measurement of serum levels: a report from the Boston Collaborative Drug Surveillance program. *Ann Intern Med.* 1974;80:516–519.
- [9] Atkinson AJ, Jr, Nordstrom K. The challenge of in-hospital medication use: an opportunity for clinical pharmacology. *Clin Pharmacol Ther.* 1996;60:363–367.
- [10] Shenfield GM. Therapeutic drug monitoring beyond 2000. *Br J Clin Pharmacol.* 2001;52(Suppl 1):3S–4S.
- [11] Ensom MH, Davis GA, Cropp CD, Ensom RJ. Clinical pharmacokinetics in the 21st century: does the evidence support definitive outcomes? *Clin Pharmacokinet.* 1998;34:265–279.
- [12] Carrico JM. Human Genome Project and pharmacogenomics: implication for pharmacy. *J Am Pharm Assoc.* 2000;40:115–116.
- [13] Collins FS. Shattuck lecture: medical and societal consequences of the Human Genome Project. *N Engl J Med.* 1999;341:28–37.
- [14] Knapp KK. The Human Genome Project. APhA 2000-American Pharmaceutical Association Annual Meeting. [Cited 2000 Jun 2].
- [15] Venter JC, Adams MD, Myers EW, et al. The sequence of the human genome. *Science.* 2001;291:1304–1351. [f1]
- [16] Gross AS. Best practice in therapeutic drug monitoring. *Br J Clin Pharmacol.* 2001;52(Suppl 1):5S–10S.
- [17] Dipiro JT, Spruill WJ, Blouin RA, et al. Lesson 1: introduction to pharmacokinetics and pharmacodynamics. In: Dipiro JT, editor. *Concepts in Clinical Pharmacokinetics.* 3rd ed. Bethesda: ASPS; 2002.
- [18] Bochner F, Tonkin A. The clinician and therapeutic drug monitoring in the 1990s. *Med J Aust.* 1993;158:422–426.
- [19] Reynolds DJ, Aronson JK. ABC of monitoring drug therapy: making the most of plasma drug concentration measurements. *BMJ.* 1993;306:48–51.
- [20] Aronson JK, Hardman M. ABC of monitoring drug therapy: measuring plasma drug concentrations. *BMJ.* 1992;305:1078–1080.
- [21] Cristodorescu R, Deutsch G, Dragan S. Clinical utility of plasma digoxin measurements. *Med Interne.* 1989;27:25–32.
- [22] DeVore KJ, Hobbs RA. Plasma digoxin concentration fluctuations associated with timing of plasma sampling and amiodarone administration. *Pharmacotherapy.* 2007;27:472–475.
- [23] Levy G. Pharmacologic target-mediated drug disposition. *Clin Pharmacol Ther.* 1994;56:248–252.
- [24] Vozeh S. Cost-effectiveness of therapeutic drug monitoring. *Clin Pharmacokinet.* 1987;13:131–140.
- [25] Spector R, Park GD, Johnson GF, Vesell ES. Therapeutic drug monitoring. *Clin Pharmacol Ther.* 1988;43:345–353.
- [26] McInnes GT. The value of therapeutic drug monitoring to the practising physician: an hypothesis in need of testing. *Br J Clin Pharmacol.* 1989;27:281–284.
- [27] Sjoqvist F. Interindividual differences in drug responses: an overview. In: Rowald M, Sheiner LB, Steiner JL, editors. *Variability in Drug Therapy.* New York: Raven Press; 1985. pp. 1–10.
- [28] Bowers LD. Analytical goals in therapeutic drug monitoring. *Clin Chem.* 1998;44:375–380.
- [29] International conference on harmonization of technical requirements for registration of pharmaceuticals for human use. *Fed Regist.* 1996;61:9315–9320.

- [30] Winter ME. Part 1: interpretation of plasma drug concentration. In: Winter ME, editor. *Basic Clinical Pharmacokinetics*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2004. pp. 73–96.
- [31] Glazko AJ. Phenytoin, chemistry and methods of determination. In: Levy RH, editor. *Antiepileptic Drugs*. 3rd ed. New York: Raven press; 1989. pp. 159–176.
- [32] Steijns LS, Bouw J, van der Weide J. Evaluation of fluorescence polarization assays for measuring valproic acid, phenytoin, carbamazepine and phenobarbital in serum. *Ther Drug Monit*. 2002;24:432–435.
- [33] Patel JA, Clayton LT, LeBel CP, McClatchey KD. Abnormal theophylline levels in plasma by fluorescence polarization immunoassay in patients with renal disease. *Ther Drug Monit*. 1984;6:458–460.
- [34] Hicks JM, Brett EM. Falsely increased digoxin concentration in samples from neonates and infants. *Ther Drug Monit*. 1984;6:461–464.
- [35] Frank EL, Schwarz EL, Juenke J, et al. Performance characteristics of four immunoassays for antiepileptic drugs on the IMMULITE 2000 automated analyzer. *Am J Clin Pathol*. 2002;118:124–131.
- [36] Wu SL, Li W, Wells A, dasgupta A. Digoxin-like and digitoxin-like immunoreactive substances in elderly people: impact on therapeutic drug monitoring of digoxin and digitoxin concentrations. *Am J Clin Pathol*. 2001;115:600–604.
- [37] Steimer W, Muller C, Eber B. Digoxin assays: frequent, substantial and potentially dangerous interference by spironolactone, canrenone and other steroids. *Clin Chem*. 2002;48:507–516.
- [38] Somerville AL, Wright DH, Rotschafer JC. Implication of vancomycin degradation products on therapeutic drug monitoring in patients with end- stage renal disease. *Pharmacotherapy*. 1999;19:702–707.