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Biopharmaceutical Considerations and Therapeutic Drug Monitoring-A Review

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Abstract

Therapeutic drug monitoring (TDM) is a strategy that may help to optimise dosing. This study examined the utility of therapeutic drug monitoring (TDM) of various drugs. Systematic plasma concentrations monitoring of the drug in keenness of potential clinical failures of treatment is known as therapeutic drug monitoring. Therapeutic drug monitoring (TDM) is recommended for medications with high inter-individual variability, narrow therapeutic index drugs, possible drug-drug interactions, drug toxicity, and sub- therapeutic concentrations, as well as to assess noncompliance. The area under the plasma concentration-time curve (AUC) is a significant pharmacokinetic parameter since it calculates the drug's total systematic revelation in the body. However, multiple blood samples from the patient are required to calculate the area under the curve (AUC), which is inconvenient for both the patient and the healthcare professional. TDM was to be deemed useful if it could be used for predicting the effectiveness of a drug and/or the occurrence of adverse reactions.

Key Words: Therapeutic drug monitoring (TDM), plasma concentrations, therapeutic index drugs (TI), area under the plasma concentration-time curve (AUC), adverse reactions.

CONCEPT OF THERAPEUTIC DRUG MONITORING (TDM)

The concept of TDM started in 1970 with the basic principle based on the fact that some drugs show a close relationship between the plasma level of the drug and its clinical effect. There exists a very little value for TDM if such a relationship does not exist. The measurement of plasma level is justified only when the information provided is of potential therapeutic benefit.

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

Clinical pharmacists and pharmacologists use pharmacokinetic principles to assess these interpretations. The science of TDM introduced a new aspect of clinical practice in the 1960s with the publication of initial pharmacokinetic studies linking mathematical theories to patient outcomes.

TDM is critical for drugs that have a narrow therapeutic index when there is no easy way to measure outcomes, the drug has severe side effects, there is an association between drug concentrations and effect and/or side effects, there exists a large variation in drug exposure

among patients receiving a fixed dose, and when several endogenous and exogenous factors alter the drug exposure in a patient.

Biopharmaceutics is the study of the physicochemical properties of the drug and the drug product, in vitro, on the bioavailability of the drug, in vivo, to produce a desired therapeutic effect. Biopharmaceutics links the physical and chemical properties of the drug and the drug product to their performance, in vivo. A primary concern in biopharmaceutics is the bioavailability of drugs. Bioavailability refers to the measurement of the rate and extent of active drug that becomes available at the site of action.

Clinical pharmacokinetic studies are performed to examine the absorption, distribution, metabolism, and excretion of a drug under investigation (investigational drug and approved drug) in healthy volunteers and/or patients. Data obtained from such studies are useful for the design and conduct of subsequent clinical trials. They are also necessary for appropriate analysis and evaluation of the efficacy and safety data obtained in clinical trials for new drug development and in post-marketing clinical trials. The results of non-clinical pharmacological and toxicological studies should be evaluated in conjunction with the results from non-clinical and clinical pharmacokinetic studies to provide useful information for the appropriate and safe conduct of clinical trials and for the evaluation of the mechanism of action in human subjects.

Recommendation of an appropriate drug regimen takes into account the patient's individualized pharmacokinetics and clinical condition or response. The following are important considerations to ensure an optimum TDM service in any setting:

(1) Measurement of patient's serum or blood drug concentration (SDC) 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.

PURPOSE OF THERAPEUTIC DRUG MONITORING

Performing TDM requires a multidisciplinary approach. Accurate and clinically meaningful drug concentrations are attainable only by complete collaboration by a TDM team, typically comprised of scientists, clinicians, nurses, and pharmacists. Excellent communication among team members is necessary to ensure that best practices in TDM are achieved. The indications for drug monitoring have widened to include efficacy, compliance, drug-drug interactions, toxicity avoidance, and therapy cessation monitoring. The indications for drug monitoring have widened to include efficacy, compliance, drug-drug interactions, toxicity avoidance, and therapy cessation monitoring.

A diagnosis is made -----A drug is selected------ - Dosage schedule is designed to reach a target plasma concentration--------- Drug is administered----------Patient assessments are performed ------Drug concentration are determined------- A pharmacokinetic model is applied and clinical judgment is used---------- If dosage adjustment necessary.

SIGNIFICANCE OF TDM

Measuring plasma concentrations may be helpful, however, as a low measurement reflects either poor recent compliance or undertreatment. Poor compliance is implicated if the patient is prescribed a dose that is unlikely to be associated with a measured low concentration or if a previous measurement suggested that the plasma concentration should be higher for the given dose.

TDM is indicated in the following clinical situations:

1. Serious toxicity coupled with a poorly defined or difficult to detect clinical end point (e.g., Anticonvulsants and Cyclosporins).
2. A steep dose response curve for which a small increase in dose can result in a marked increase in desired or undesired response (e.g., Theophylline).

3. A narrow therapeutic range (e.g., Digoxin).
4. Marked inter-individual pharmacokinetic variability, which increases the variability in the relationship between dose and plasma dose concentration (e.g., Phenobarbital).
5. Non-linear pharmacokinetics which may lead to rapid accumulation of drugs to toxic concentration (e.g., Phenytoin, Phenobarbital).
6. An unexpected toxicitydue to drug interactions (Egenrofloxacin induced Theophylline toxicity, or Chloramphenicol or Clirazepate induced Phenobarbital toxicity).

MEASURING PLASMA DRUG CONCENTRATION IN THERAPEUTIC DRUG MONITORING

The contribution of pharmacokinetic variability to differences in dose requirements can be identified by measuring the drug concentration at steady state and modifying the dose to attain a desired concentration known to be associated with efficacy. However, there is substantial inter-individual pharmacodynamic variability at a given plasma concentration, hence a range of concentrations rather than a single level is usually targeted. For a limited number of drugs for which there is a better relationship between plasma or blood concentration-response than dose-response, the measurement of plasma or blood concentrations has become a valuable surrogate index of drug exposure in the body.

ANALYTICAL ISSUES IN THERAPEUTIC DRUG MONITORING

As stated previously, the practice of therapeutic drug monitoring requires the orchestration of several disciplines, including pharmacokinetics, pharmacodynamics, and laboratory analysis. The analytical impact on determining pharmacokinetic parameters is not well appreciated. Analytical goals in therapeutic drug monitoring should be established by determining the nature of the problem to be solved, selecting the appropriate matrix and methodology to solve the problem, and developing valid analytical schemes that are performed competently with appropriate quality and interpreted within the framework of the problem. If plasma drug concentration measurements are to be of any value, attention must be paid to the timing of blood sampling, the type of blood sample, the measurement technique, and the interpretation of results. First, it is vital to obtain the blood sample for measuring the drug concentration at the correct time after dosing. Errors in the timing of sampling are likely responsible for the greatest number of errors in interpreting the results.

PRACTICAL ISSUES IN THERAPEUTIC DRUG MONITORING

Ideally, a quality drug assay should be performed within a time frame that is clinically useful. In large chemical pathology laboratories staffed by highly skilled scientists and equipped with state-of-the art automated analyzers, many clinicians assume that the results will be accurate. Therefore, analytical laboratories should ensure that procedures are in place to obtain any missing information from the drug assay request that may be needed for appropriate clinical interpretation of the results, such as dosage regimen, time of blood sampling, and that the accuracy, precision, sensitivity, and specificity of each assay is documented and assessed regularly. Wherever possible, the assay performance should be evaluated using an external quality assurance program that provides a rapid turn-around time for results and comprehensive feedback on the assay performance, and that has a large number of subscribers.

Table 1: MOST COMMONLY MONITORED DRUGS IN TDM

Sl No	Categories	Drugs
01	Cardiac glycoside	Digoxin, Digitoxin
02	Antiarrhythmic	Lidocaine, Quinidine, Procainamide, N-acetylprocainamide, Disopyramide, Amiodarone, Propranolol
03	Antiasthmatic	Theophylline
04	Antiepileptic	Carbamazepine, Etosuximide, Phenobarbital, Phenytoin, Primidone, Valproic acid, Benzodiazepines,
05	Antidepressant	Imipramine, Amitriptylinr, Clomipramine, Trimipramine, Doxepine, Desipramine, Nortryptalline, Maprotiline, Protryptiline, Lithum

06	Antineoplastics	Methotrexate
07	Immunosuppresants	Cyclosporine, Tacrolimus
08	Anticoagulant	Warfarin
09	Antibiotics	Gentamycin, Amikacin and Tobramycin

CONCLUSION

The concept of TDM and its services are new in our country and it may not be essential for all categories of drugs, but whenever specialized treatments are offered in super specialty hospitals for chronic conditions, the TDM is an effective and valuable service. TDM is a useful adjunct in treating many patients provided the potential pit falls and harms are considered. The use of TDM requires a combined approach encompassing pharmaceutical, pharmacokinetic, and pharmacodynamic techniques and analyses. The appropriate use of TDM requires more than a simple measurement of patient blood drug concentration and a comparison to a target range. Rather, TDM plays a significant role in the improvement of safe and effective therapeutic medications and individualization of these medications.

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