

4. THERAPEUTIC DRUG MONITORING

Therapeutic drug monitoring (TDM) is a process that involves the measurement of drug concentration in body fluids preferably blood plasma for the management of dosage regimen in an individual patient. This process has been successfully used in the adjustment of dosage because this concept act as a key to interlink the plasma drug concentration with clinical effects and toxicity produced by the administered drug. Although to exert optimal clinical effects by a drug with minimal side effects/toxicity, drugs plasma concentration needs to be maintained within certain range of concentrations and this range can be referred as therapeutic range. Each drug has different and specific therapeutic range. Therapeutic range of some drugs are as given a) Phenytoin 10-20 mcg/ml, b) Quinidine 1-4 mcg/ml, c) Amikacin 20-30 mcg/ml, d) Digoxin 1-2 ng/ml, e) Vancomycin 20-40 mcg/ml, f) Lidocaine 1-5 mcg/ml, g) Carbamazepine 4-12 mcg/ml. If the plasma concentration of the drug remains within this range, there are maximum chance that patient is receiving safe and effective treatment. But if the plasma concentration deviates out of the therapeutic range, safety and the effectiveness of the dosage regimen cannot be ensured. So TDM act as evaluating tool to evaluate the clinical response of the patient exerted by the prescribed dosage regimen. Using the results of performed TDM, reasons of the deviation of the patient response to the therapy can be justified and best modification in the dosage regimens can be done to provide the maximum clinical benefits to the patient. With enhanced awareness in management of therapy from past decade, TDM has become the part of standard clinical care system.

Indications for TDM

Although TDM can add safety to the drug therapy of a patient but has limited evidences in improving therapeutic response of the drug in patients. TDM is basically a expensive process so decision of conducting TDM should be taken carefully. Even TDM is not required for all the drug and in all the therapeutic circumstances. Therefore, the TDM should be performed with an appropriate indication as mentioned below:

- Most importantly if the evaluation of clinical response of prescribed drug therapy in a patient is not possible due to lack of measurable clinical parameters such as vital signs, symptoms or laboratory investigations of patients. In this situation best mode to monitor the effectiveness of the drug therapy is TDM. For example, TDM is useful for anticonvulsant drugs.
- TDM is also beneficial in the case of drug toxicity to ensure that the maintained average steady state concentration of the drug lies within the therapeutic range or not
- TDM is of great importance for the drugs belonging to narrow therapeutic index where the chances of occurrence of drug related toxicity is high. So to reduce the risk of toxicity TDM may be performed to provide safer drug therapy. For example, dioxin, lithium, vancomycin.
- TDM is indicated also for the drugs which show unpredictable pharmacokinetic behavior because some drugs follow nonlinear pharmacokinetics. For example, phenytoin.
- TDM is also suggested for the assessment of patient medication compliance.
- As the TDM involves the drug assays, it is also indicated in identification of poisons, severity of poison and in monitoring of poison excretion from the body.
- To provide assistance in modification of dosing regimen of patient using specific pharmacokinetic information related to concern drugs and patient.

Protocol for TDM

Decision for TDM: First of all, it is very important to justify that conduction of TDM for a specific drug in that particular clinical situation is appropriate or not. The accurate judgment about the need of TDM should be based upon the indications as discussed earlier in this chapter. Further it also depends upon the patient's response to initially prescribed dosage regimen. If patient do not respond as expected, the clinical situation can be assessed for need of TDM by the healthcare team.

TDM Request: After the confirmation of TDM requirement for a drug in a patient. It is requested on TDM form to be filled by concern healthcare professional. The information specific to patient, prescribed dosage regimen and related clinical situation is required for TDM, form which later provide help in interpretation of TDM results.

TDM ORDER FORM/ TDM REQUEST	
Hospital _____	Date: _____
Patient's Information	
Age _____	Gender _____
Weight _____	Ward _____
Clinical situation/ Reason for request	
Suspected Toxicity _____	Drug Interaction _____
Poisoning _____	Lack of Clinical Response _____
Others _____	
Comorbidities _____	
Dosage regimen Information	
Name of Drug to be assayed _____	Dose/Freq. _____
Dosage Form _____	Route _____
Duration _____	Time/date of last dose _____
Time and date of sampling _____	
When result needed, immediately, Within 2-4 hrs, Within 24 hrs.	
Doctor's Signature _____	Date _____
Contact _____	

Figure representing example of TDM order form

Sampling: Different types of biological fluid may be collected from the patient as samples to perform TDM. The type of biological sample to be collected mainly depends on the stability of drug in that particular sample. For most of the drugs whole blood, plasma or serum are collected as samples. For some of the drugs, urine and saliva may be collected but must be analyzed using highly sensitive method. Drug characteristics and type of analytical method opted determines the type of anticoagulant used, vessel used for collection, storage conditions, duration of which sample can be stored.

Time of Sampling: Plasma Drug concentration constantly keeps on changing during a therapy of multiple dosage regimen. Frequent ups (crests) and downs (Troughs) in the plasma drug concentration are observed throughout the day as consequences of specific pharmacokinetic behavior and designed dosing regimen of the drug. Therefore, the sampling time in TDM is also very crucial and should be done carefully. Commonly sampling in case of the drug with short-half life should be done in trough region that is just before the time of next dose, Where, as the sampling in case of the drug with long half-life can be done any time after the completion of drug distribution. Except drug toxicity, poisoning and few emergency situations sampling in TDM should be preferably done after the achievement of steady state plasma drug concentration.

Drug Analysis: Development in the drug analytical techniques such as improved accuracy, high sensitivity, more specificity and less time consumption, leads the extensive use of TDM in therapeutic. Presently most of the drugs are assayed using automated methods such as ELISA (enzyme linked immunoassay, FPIA (fluorescence polarization immunoassay). Other best techniques used in drug analysis are HPLC (High-performance liquid chromatography, UPLC (Ultra-performance liquid chromatography) which need small sample preparation time. GLC (Gas liquid chromatography), GC are also used for the analysis of volatile samples. Combined approaches like LC-MS of the above mention techniques also have their own advantages in determining drug concentration in various biological samples collected for TDM.

Communications of TDM Results: TDM results must be conveyed to the healthcare team of the patient as soon as possible. More preferably it should be conveyed before the administration of next dose so that required modification in the current dosage regimen can be done immediately to provide safer and more effective treatment to the patient. Generally used methods are via telephonic, hard copy reports, online reporting software systems.

Assessment and Adjustments: After receiving the TDM drug assay results, concern healthcare team have to make a necessary assessment of possible causes for unexpected outcomes like medication errors hypersensitivity, drug interactions, non-compliance, pharmacogenetic variations. Identification of appropriate unexpected outcome will help to make adjustment in the dosage regimen and improve health related quality of life in patient. The clinical pharmacist can play a key role in TDM team by suggesting best use of TDM using his collective knowledge in the field of drug analysis, clinical pharmacokinetics and therapeutics.

Limitations of TDM

TDM is expensive, time consuming process where only the highly trained and skilled healthcare professionals can contribute in the overall conduction. Very specific, selective, accurate and validated drug analytical techniques are required in this process. As discussed earlier it is only possible for limited number of drugs. Non allopathic medicines, nutritional deficiencies and formulation variations interfere to contribute alteration in pharmacokinetics of the drugs which can give rise to deviations in TDM results.

Clinical Situations in TDM

As TDM is used to evaluate clinical response of a patient by measuring blood drug concentrations, so on the bases of these blood drug concentrations levels various type clinical situations can be seen while performing the TDM in patients with different clinical response. Expression of clinical situation and their managements are described in table as shown.

Table 4.1: Clinical situations and their management in patient with lack of clinical response

Sr. no.	Clinical Situations	Management
1	If observed blood drug concentration (In TDM result) is below therapeutic range	Check adherence, if adherent increase the dose
2	If observed blood drug concentration (In TDM result) is within therapeutic range	Check adherence, small increase in dose can be considered otherwise change the therapy
3	If observed blood drug concentration (In TDM result) is above therapeutic range	Diagnose again or change therapy

Table 4.2: Clinical situations and their management in patient with normal clinical response

Sr. no.	Clinical Situations	Management
1	If observed blood drug concentration (In TDM result) is below therapeutic range	Maintain same dose or review the therapy
2	If observed blood drug concentration (In TDM result) is within therapeutic range	Maintain the same therapy
3	If observed blood drug concentration (In TDM result) is above therapeutic range	Assess patient for toxicity and reduce the dose as required

Table 4.3: Clinical situations and their management in patient with hyper clinical response and drug toxicity suspected.

Sr. no.	Clinical Situations	Management
1	If observed blood drug concentration (In TDM result) is below therapeutic range	Possibility of laboratory or sampling error so repeat the process, other explanations for toxicity can be considered
2	If observed blood drug concentration (In TDM result) is within therapeutic range	Look for other possible reasons that can cause toxicity
3	If observed blood drug concentration (In TDM result) is above therapeutic range	Stop the therapy, can be started with low dose.