

# Role of clinician in therapeutic drug monitoring practice



## Abstract

Therapeutic drug monitoring is a clinical service in which to measuring different drugs in different time periods to manage a desired concentration of drugs in the patient's blood. Clinicians approach the laboratory to monitor drug concentration to minimize toxicity and enhance therapeutic responses. The clinician manages the cases of a drug overdose and decides how to recoup drug toxicity with limited pharmaceutical requirements and figure out patient consent along with treatment. The main purpose of TDM is to use appropriate blood drug concentrations that possess a narrow therapeutic spectrum in order to optimize the clinical results. This review summarizes the key concept of therapeutic drug monitoring, its historical background, pharmacokinetic principles, the role of clinician and its future scope of TDM in clinical practice.

**Keywords:** therapeutic drug monitoring (TDM), clinical service, HPLC

## Introduction

Therapeutic drug monitoring service is a branch of clinical pharmacology and clinical pharmacy which is specific to a measure of the drug concentrations in patient's blood e.g. serum, plasma and saliva. The main goal is the optimization of the dosage regimen which can provide adequate and safe drug therapy through maintaining blood drug concentrations within a therapeutic range or window [1]. The therapeutic range has usually described the range of doses that produces a therapeutic response without causing any adverse effect. The therapeutic window is a ratio which provides maximum therapeutic concentrations with minimum toxic concentration. The major aim of TDM is to maintain plasma drug concentrations within a predetermined range in order to optimize treatment outcome since concentrations above reference values are generally linked to the increased side effects, whereas those below the reference values would lead to ineffectiveness or unsatisfactory response [2].

## Historical Background

TDM was introduced in the 1960s, on epileptic patients, the researcher showed a clinical correlation between plasma concentration of

phenytoin in epileptic patient's. 1967s Baastrup and Schou showed a pharmacological effect of lithium in the plasma sample. However clinical pharmacokinetics rise and monitored in the late 1960 and early 1970. In the periods of 1970s TDM is focused on adverse drug reactions and reduce the incidence of toxicity and determine and ensured therapeutic ranges [2]. Recently clinical pharmacokinetics of drug monitoring raise information on drug concentration relationships, drug pharmacokinetic characteristics, and advancements in analytical technology [3]. Today TDM includes monitoring of patient compliance, drug efficacy, drug interactions, drug-food interaction and individual variation in cure response, toxic effects, as well as therapy cessation.

## Pharmacological Principles of TDM

Ironically the most essential pharmacokinetic guideline used to adjust dosage is drug half-life, the volume of distribution and excretion. Knowledge of half-life of the drug can determine the amount of drug in patient serum at any point [4]. The clinician can estimate the time of drug where it can be sub therapeutic, therapeutic, produce toxic responded and also knowing about the what time to give the

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next dose having full command on clinical pharmacokinetics. The clinicians need the volume of the distribution parameter to measure the desired dosage and adjust the serum level [5]. The factors that are usually considered in clinical settings are the first dose in milligrams/kg as per patient's body weight and steady-state serum concentration [6]. This parameter is recorded into computer software programmable and calculates the correct dose. Based on above mention parameter clinician or paramedic can calculate a new dosage and given to the patients if the clinical situation warrants it for e.g. If the serum levels are sub therapeutic and the patient's clinical situation is decline can increase the dose and observed outcome of dose. However, if the serum levels are under sub therapeutic, but the patient's clinical condition is improving, dosage change would not be a change in dose would not be required [6].

Combining knowledge of pharmacokinetics, pharmacodynamics, and pharmaceuticals in drug monitoring service is facilitated and ensures to enhance the effectiveness and safety of specific drugs in a different type of clinical context. Pharmacokinetic variability plays an important role in dose requirements and adjustment that can be investigated by measuring the drug concentration and alter the dose to obtain desired concentration which associated and provide safety and efficacy. Factors include consent, medication error, and drug interactions [7]. Moreover, the measurement of drug therapy is an exclusive section that provides drug concentration and interpretation on the basis of based on pharmacokinetic parameters. Clinician interpretation of a drug concentration is to ensure to provide an excellent therapeutic response that will clinically benefit for patients [8,9].

Clinicians commonly observed drug pharmacodynamics through the physiological

indication of therapeutic responses like lipid test monitoring, blood glucose and blood pressure, as well as coagulation profile [10]. The process of TDM is anticipated that obvious relation occurs between drug dose and blood drug concentration with pharmacological effect. Blood drug concentration can guide the clinician to stop treatment in two common circumstances. The first treatment should stop if the plasma drug concentration is lower than the therapeutic range in a patient whose clinical condition is satisfactory. Second, when the plasma drug concentration is at the higher limit and absence of any clinical effect, then increased dosage is unlikely to be favorable and the toxicity is at higher risk. The exit of this drug and the use of specific treatment would be appropriate [11].

### Criteria for TDM

Not all drugs can be monitored under TDM service **TABLE 1** Common monitored drug.

Following fundamental which must be followed might be the following:

1. The direct correlation between patient's response to the drug and plasma drug concentration
2. The pharmacokinetics of drugs must have been established and routine range is convenient for the prognostic pharmacokinetic criteria
3. The drug must be measurable in fewer blood samples by the diagnostic method. The method is specific for the drug and able to separate it from other similar aggregates including its metabolites
4. Cost-effectiveness [12]

### Essentials of TDM

Therapeutic drug monitoring service is established when the first drug dose prescribed, and comprise determining in a first dosage regimen relevant for the clinical status and

**TABLE 1. Commonly monitored drugs in TDM.**

	Class	Drugs
1	Cardiac glycoside	Digoxin, Digitoxin
2	Antiarrhythmic	Lidocaine, Quinidine, Procainamide, Disopyramide, Amiodarone, Propranolol
3	Antiasthmatics	Theophylline <sup>13</sup>
4	Antiepileptic	Carbamazepine, Etosuximide, Phenobarbitol, Phenytoin, PrimidoneValoproic acid, Benzodiazepines
5	Antidepressant	Imipramine, Amitriptyline, Clomipramine, Trimepramine, Doxepine, Desipramin, Nortryptiline, Protryptiline, Lithium
6	Antineoplastic	Methotrexate
7	Immunosuppressant	Cyclosporine, Tacrolimus
8	Anticoagulants	Warfarin
9	Antibiotics	Gentamycin, Amikacin, Tobramycin, Vancomycin <sup>14</sup>

patients further aspects such as age, weight, organ and other complementary with drug therapy [13-15]. Other monitoring facts that should be examined include sampling time related to drug dose, history, patient response and the desired drug targets [16].

In addition, following must be taken care:

1. Accurate dispensing of drugs with total daily dose and dose intervals
2. Record of accurate time of administration
3. Correct sampling time
4. Correct Assay method
5. Patients clinical status (Acute/Chronic disease)
6. Co-morbid
7. Concurrently administered drugs
8. Indications

## Necessity of TDM

### ■ TDM is necessitated in following clinical situations

1. Serious toxicity with poorly defined end point e.g., Anticonvulsants, Cyclosporine [17]
2. Steep dose-response curve e.g. theophylline
3. A narrow therapeutic window e.g. Digoxin
4. Pharmacokinetic variability e.g. Phenobarbital
5. Non-linear pharmacokinetics with the rapid accumulation of drugs to toxic level e.g. Phenytoin, Phenobarbital [18]
6. Unexpected toxicity due to drug interactions
7. Long term drug therapy e.g. Anticonvulsants [19]
8. In life-threatening situations Epilepsy or Sepsis [20]

## Unnecessity of TDM

1. The clinical result is inappropriate either to dose or to plasma concentration
2. Dosage use without discriminate
3. The pharmacological effects can be clinically evaluated
4. Drug and blood drug concentration relationship remains obscure established
5. A wide therapeutic range like beta-blockers and calcium channel blockers [21]

## Analytical Method of TDM

Different analytical methods and assays are established from the drug monitoring service. Radioimmunoassay is one of the oldest methods but now a day's it's not applicable due to their hazardous waste. High-Performance Liquid Chromatography (HPLC) is used for the determination of drug concentration in research laboratories. Maximum drug assays performed in the clinical laboratories are commercially available immuno binding assays methods. The other techniques include Fluorescence Polarization Immuno Assay (FPIA), Enzyme Immunoassay (EMIT), enzyme-linked Immunosorbent assay and Chemiluminescence assay currently worked for [22,23]. The above mention assays are capable to identify other metabolites or drug-related substances these methods work on the antigen-antibody method. It can also show cross-reactivity results with the drug and its metabolites, due to similar structures of drugs indicate false negative or false positive results [24].

The general characteristics of analytical methodology should ideally be the following:

1. The method should be able to differentiate between drugs and similar structures of the compound
2. Able to encounter less quantity
3. Sample sufficient to be used as a routine assay
4. Unaffected with the other drugs being carried out simultaneously [25]

## Role of Clinician in TDM Practice

Drug monitoring service has gained tremendous popularity among the clinicians, clinical pharmacist and paramedical staff in the past two decades. Clinicians interpreted the result and select the correct drug and dosage as per the patient's needs. Clinician used TDM as a treatment guideline and get excellent therapeutic result with less toxic effects can be obtained. TDM is an essential tool to recognize and determining a blood or serum level whether it is in therapeutic, sub-therapeutic or toxic ranges. It encompasses consideration at a serum level in relation to the patient's clinical outcome drug profile, and scientific history to determine if a change of dosage is necessary [26]. Clinicians send TDM form that has all history of the patient along with blood samples to the laboratory for measuring drug concentration in patient blood or plasma. After all, clinicians have to treat patients not the serum levels [27].

## Reasonability of TDM

The clinician uses TDM for a variety of reasons not only for diagnosis determination as well as treatment. Some of the important parameters are described below:

### ■ Monitor overdose

Therapeutic drug monitoring is one of the important platforms which facilitate the clinician to identifying drug overload and follow the progress of treatment execute to the patient e.g. Acetaminophen is a metabolite that works in both as non-reactive and certain cases as reactive metabolites. That drug is working as non-reactive metabolites which become reactive metabolites and increasing the production of drugs which is responsible for the toxicity of the drug. E.g. liver toxicity is associates with acetaminophen overdose. To access the blood level in appropriate time interval administration, the clinician can refer the patient to evaluate the chance of liver toxicity [28].

### ■ Patient's social behaviour

Patient's social behaviour like smoking and drinking can also affect the serum levels of medications. e. g. Smoker patients having theophylline can eliminate the drug from the body as faster than a non-smoker. It's observed that smoker's patient needed higher dosages of theophylline than non-smokers [29]. Patients along heart failure excrete of theophylline is less than normal patient hence it's elevated serum levels of drug than the normal patient [30]. Usually, drug blood levels are high in some medications include vancomycin, aminoglycosides, and digoxin, which are excreted predominantly from the kidneys.

### ■ Reduce toxicity

Clinicians prescribe drug levels to minimize the adverse effect of drug reactions especially for the narrow therapeutic drug (a narrow therapeutic drug which small amount in the higher side can cause toxic effect and lower side can cause sub-therapeutic effect). Example of drugs is digoxin, lithium; aminoglycoside antibiotics include gentamycin, tobramycin, and amikacin, phenytoin, and theophylline. Execute the daily dosage of aminoglycosides can improve patient outcomes and reduces toxicity. The recommendation is to check drug peak and trough level, but clinically trough level is recommender then peak level [31].

### ■ Minimize dosages

The clinician may also order TDM to the measurement of drug blood concentration and try to minimize dosage with maximized therapeutic response in favour of a patient's health. E.g. aminoglycoside antibiotics concentrate in the urinary tract infection is recommended [32].

### ■ Active metabolites

The clinician may also use TDM to monitor drug levels to identify the clinical output of active metabolites. Therapeutic drugs present special problems when these drugs are metabolized to compounds that are active pharmacologic and some metabolites that have a similar structure to of parent drug. During monitoring of serum drug level that metabolites show false-negative results and may apparently increase obtained plasma levels [15].

### ■ Drug-drug interaction

Two and more drugs interact with each other than the comprehensive outcome of one and others taking the drug may be larger than desired. E.g. Aspirin is used to make blood thin and warfarin is used to treat against heart attack and inhibit blood clots from inside heart vassal. The particular drugs together may induce excessive bleeding. The reaction of one or both of the drugs may be less than desired.

E.g. some antacids can inhibit some drugs include antibiotics, blood coagulants, and heart medication. In those cases, the drugs may not work properly or not work at all.

Vitamins and minerals are also good examples of drug-drug interaction because they have the ability to react with other drugs and decrease the therapeutic effects. e. g. Iron supplements are a good example that blocks the effect of other antibiotics and decreases their activity. Some of the routine foods like grapefruit juice can block the activity of some drugs so the medicine may stay in your body longer. Some alcoholic beverages can also show high interaction with many drugs and can be especially dangerous to use with stimulants, sedatives, sleeping pills, and painkillers to avoid taking these beverages together with any medicine. Antacid medications can change the ph. of gastrointestinal will be able to change the absorption of other medications such as digoxin and phenytoin to decrease their pharmaceutical effect if taken together with antacid [33].

## ■ Drug-food interaction

The interaction between food drugs can also lead to the adverse impact of drug therapy. Food-drug interaction is also reduced or stops the pharmaceutical effect of drugs. E.g. drug and food route of administration by the mouth and it is absorbed through small intestine if the food particle is present in the stomach lining it will reduce the absorption of the drug. Generally, patients are on medication avoided taking drugs one hour before and two hours after a meal. Food decreases the pharmacokinetic of drugs such as theophylline sprinkle, a form on sustained-release theophylline intended to provide long term relief its absorption can be significantly altered by the presence of food in the stomach, so monitoring of serum levels can guide its time of administration related to food intake [34].

## Factor Affecting on TDM

The most important factors that must be considered while prescribing a TDM include:

### ■ Blood sample timing

Appropriate timing of a blood sample plays an important role while ordering TDM. Proper timing is an essential tool in TDM. All drugs which are considered under TDM service have to take at their recommended timing. Some TDM drug timing is mentioned below [8].

1. Carbamazepine: The Half-life can be longer than 48 hours ensuring a single dose. Recommended is a trough concentration just after the dose followed by a peak level 3 hours later
2. Digoxin: Guidance for sample six hours after a dose is recommended to escape inappropriate concentrations
3. Gentamycin: Pre-dose and peak (0.5 hours after I.V. and 1 hour after intramuscular administration)
4. Lithium: 12 hours sample gives the most appropriate guide to dose adjustments
5. Phenobarbitone: Any time sample can be taken, timing is not crucial
6. Phenytoin: It has a long half-life so the timing of concentration monitoring is not critical
7. Theophylline: has a narrow therapeutic range and timing of the sampling is not critical if the patient is receiving one of the slow-release preparations [35]

Generally, TDM utilized at the beginning of drug treatment and allow clinicians to bypass toxic plasma levels. In the majority of cases, the toxicity of drugs can be interpreted clinically, e.g. phenytoin is easy to recognize toxicity, and TDM may not be necessary for the diagnosis of phenytoin toxicity. However, TDM is a truly helpful guide and regulate phenytoin dosage subsequently [36], digoxin is given patient for heart disease and toxicity is easily suspected in plasma level. And it is necessary to confirm toxicity. Indications for plasma drug concentration measurements have some appropriate criteria which include timing of blood or serum sample, specify vacutainer tube for specific drug shown in **TABLE 1**. Accurate drug measurement is possible only by a TDM team based on clinicians, nurses, and pharmacists. With the help of collaboration as well as communication among TDM team members is necessary to ensure best practices in TDM [21].

### ■ Effect of age

The clinician will treat the largest numbers of geriatric patients in different populations. Being treated simultaneously for more than one condition with various prescription drugs and they are at greater risk of adverse drug reactions. The need for a clinician to minimize the incidence of these reactions has become incumbent on both clinicians and administrators. Geriatric patients are more sensitive to the Central Nervous System (CNS) drugs effect but less sensitive to cardiovascular effects. It is observed that children are more sensitive to the effects of morphine. However, research is still going on and required more data about the effect of the drug in age and pharmacokinetic and pharmacodynamics of drugs to allow optional individualization of dosage [37].

### ■ Effect of pregnancy

Unfortunately prescribing therapeutic drugs during pregnancy there is very short information in the literature to support this practice. Newer antimicrobials are excluding pregnant women for reasons of risk avoidance and, therefore, prescribers must rely on post-marketing surveillance data [38].

### ■ Effect on lactating mother

Although some drugs are much contraindicated during breast feeding because drugs enter in breast milk and make different concentrations, which leads to a toxic effect in the infant. Generally female use to treated in

acute and chronic infection while breast feeding. Knowledge of important drug factors to limit drug transfer and knowing where and how to find this information and provide the best cure for women and their infants. Women can be bare for many reasons to stop breastfeeding.

Some woman is not interested in breastfeeding after delivery and some stop for minor reasons. Pharmacists are in a position to select and ensure lactation and prevent inadvertent recommendations to stop breastfeeding by a less informed health care professional [39].

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### Future Scope of TDM

Therapeutic drug monitoring or TDM is apparently very useful comprehensive studies recommended that it could be more beneficial if we used with the help of proper guideline. Some of the drug concentrations come in improper timing, especially in the inpatient and it is also a concern. Hence it is the duty of paramedics to make it possible to must careful about sample timing to improve TDM quality and get the maximum therapeutic effect and neglected toxic effect. For the improvement of TDM, it is highly recommended some of the useful approaches for improving the use of TDM. One of the important approaches which really work is to arrange awareness program like conferences, lectures and newsletters, multidisciplinary quality improvement efforts, proper TDM services, can be enhanced by developing computer-based software [40]. The computerized approach holds extraordinary potential, especially to more organizations computer systems which reduce the human error and provide better and useful information via systems in a short time these approaches are effective and are complementary to be improving and practice of TDM [41].

The clinician can improve TDM service by arranging education programs to provide knowledge to the pharmacist, nurses; clinical pharmacists and with the help above all approaches to provide better results of TDM. And one more important issue is there is less no of the hospital in developing countries like Indonesia, Africa, and Taiwan and along with no TDM service at all however many of the countries have TDM service which is very expensive and beyond the reach of the common man. So clinicians on an international level must run global awareness sessions to highlight the importance of using TDM services in the management of patients. World health organization must allocate charity funds for procurement costly equipment to promote TDM service in poor countries.

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### Conclusion

Therapeutic drug monitoring is a fundamental tool in the health care sector. Coordination of Clinical team which includes clinician, paramedical staff and clinical pharmacist can enhance this practice. Concerns staff education has to be encouraged to improve the TDM services. The International Association for Therapeutic Drug Monitoring and Clinical Toxicology also participate and working in improvement in TDM services. Introducing therapeutic drug monitoring services in third world countries is the most concern point and future work should base to offer and provide all facilities to improve patient health care in poor countries for patient benefit.

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