International Journal of Medical, Pharmacy and Drug Research (IJMPD)

Article DOI: https://dx.doi.org/10.22161/ijmpd.7.1.1

Peer-Reviewed Journal Int. J. Med. Phar. Drug Re., 7(1), 2023

ISSN: 2456-8015

Understanding Therapeutic drug monitoring (TDM) at a glance

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Received: 11 Dec 2022; Received in revised form: 13 Jan 2023; Accepted: 01 Feb 2023; Available online: 28 Feb 2023

Abstract

This paper gives an overview of therapeutic drug monitoring. The primary objectives of TDM are to prevent therapeutic failures carried on by poor compliance or prescribing a drug at a dose that is too low, as well as negative or toxic effects brought on by an excessive dose. Moreover, it gives information about when and what type of drug needs therapeutic drug monitoring. Like the drug which has a short therapeutic window they require therapeutic monitoring because it can cause toxicity or no therapeutic effect. However, the appropriate use of TDM is not only the simple measurement of patient blood drug concentration and the comparison of its target range but also TDM plays an important role in the therapeutic medication by ensuring safety and effectiveness also with individualization of these medications, desired clinical targets, dosage history, sampling time in relation to the dose patient's response these factors needed to be considered while interpreting drug concentration measurements to achieve the optimal response with minimal toxicity. So TDM can be considered as a combined approach encompassing pharmaceutical, pharmacokinetic, pharmacodynamic techniques and analyses.

Keywords— *Therapeutic drug monitoring, therapeutic window, less efficiency, toxicity, blood serum level.*

I. Introduction

Therapeutic drug monitoring works to maintain serum medication concentrations within a therapeutic Range in order to provide the best possible therapeutic treatment. Here we need to keep eye on the drug concentration, specifically serum drug and plasma drug concentration. The term "Therapeutic Range" refers to a range of pharmacological concentrations where there is a relatively high likelihood of the desired clinical response and a relatively low likelihood of unacceptable toxicity(1). To summaries, therapeutic drug monitoring combines clinical medicine, laboratory technology, pharmacology, and therapeutics knowledge to determine patient-specific dosage regimens for a variety of medications in order to maximize therapeutic effectiveness while minimizing toxicity. Moreover, on the basis of that we can adjust the dose to get the best result. For example, if drug concentration exceeds the therapeutic range, then we need to reduce the dose(2). Furthermore, to understand the TDM here we discuss about the basics of TDM which helps people to understand we need to monitor the drug concentration (3). If we do not maintain what will be the consequences. However, this paper also gives idea about when TDM actually requires in a very laymen language or easy language which is easily understandable for everyone(4). Then, there is a short and important list of all the possible drugs that need therapeutic drug monitoring so that we don't need to look from different sites(5).

II. Idea of TDM

First of all, we need to know that most of the drugs have large therapeutic windows. That means a medication's effective concentration and toxic concentration are separated by a wide therapeutic window, making the drug generally safe. But there are some classes of drugs that have narrow therapeutic windows and this type of drug needs monitoring. Because this type of drug has a very short window which means they can show no efficacy or toxicity by little difference of dose. So , this type of drug requires TDM which determines the concentration of specific medications in your blood.

The green part of the picture shows the therapeutic range. Which means below this range (yellow arrow) will show no pharmacological action or no efficacy so here we need to increase dose. On the other hand, red arrow indicates that if concentration of a drug is above the therapeutic range it can cause toxic effects. So in this case we need to adjust and decrease the dose.

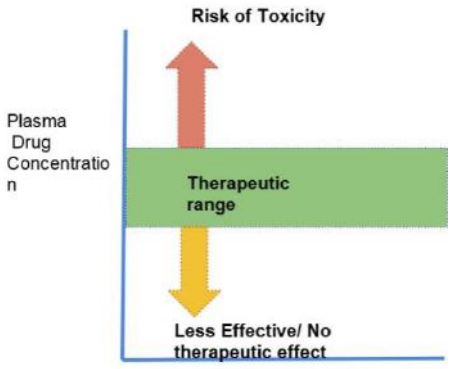


Fig 1: Idea of TDM.

When does TDM require:

If any drug has a very narrow therapeutic window we have to be very careful. So we can say that therapeutic drug monitoring is mainly focused on the drug which has a narrow therapeutic window because here we have to walk on very tight rows. As a result, we always need to keep an eye (6).

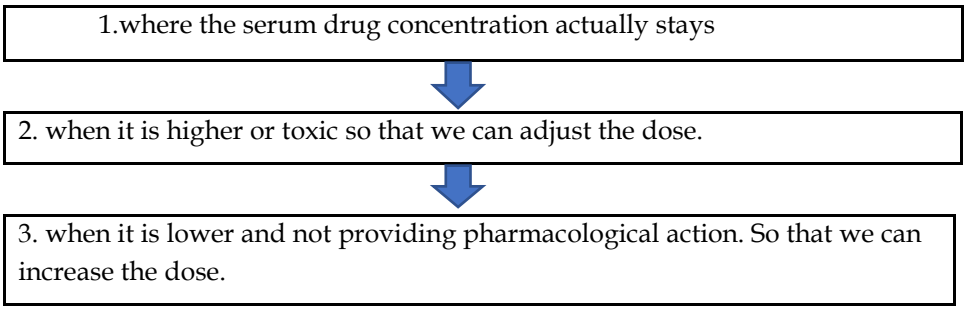


Fig 2: flowchart showing when TDM requires.

The first box of flowchart it tells us after having or administering the drug where and when our serum level of drug reaches. Then , in the second box it explains that TDM helps to know whether the dose is higher than the normal range or not. As a result, dose can be adjusted, which means we can decrease the dose to get rid from the toxicity. This is very important to know as it causes toxicity which is life threatening for us. Finally, the last requirement indicates that TDM is required to know whether the drugs show their pharmacological action or not. The dose is enough to show their activity or not otherwise we can increase the dose and get the best pharmacological actions which fulfils the goals of administering the medications.

Three Assumptions for TDM:

TDM is based on the principle that for some drugs there is a closed relationship between the plasma level of the drug and its clinical effect. that's why drugs metabolism varies from patient to patient. TDM aim to promote optimum drug treatment by maintaining serum drug concentration with in a therapeutic range. Basically when a precise therapeutic end point is difficult to define monitoring of drug levels maybe of considerable therapeutic assistance. Moreover clincian's choice of drug dosages in order to provide the optimum treatment to avoid toxicity.

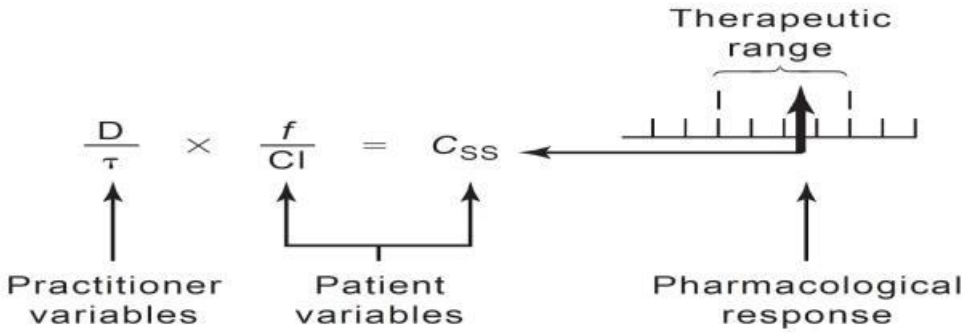
1. In case of adjusting individual drug dosage form as for variations in patient pharmacokinetics, the measuring of patient SDC is very essential as it provides a better opportunity.
2. The pharmacological response and SDCs within the patient maintain a good relationship.
3. The SDC came up with a better prediction of patient reaction or response than the dose.

Drug That Required TDM :

Drugs type	Therapeutic agents	TDM
Cardiac drug	Digoxin, digitoxin, quinidine, N-acetyl-procainamide(a metabolite of procainamide)	Value of monitoring : low The heart rate and the adverse effect whenever monitoring clinically for some drogs clinically monitoring will be more helpful than TDM(7).
Anti-cancer drug	All cytotoxic agents , Methotrexate	
Immunosuppressants	Cyclosporine, sirolimus, tacrolimus azathioprine	Value of monitoring : moderate(8)
Antibiotics/ Antibacterials	Aminoglycosides(tobramycin, gentamicin, amikacin), Glycopeptide (vancomycin)	value of monitoring :high To avoid toxicity in elderly, infant and patient of cystic fibrosis monitoring is essential to achieve therapeutic effect(9). value of monitoring vancomycin : moderate
Bronchodilators	Caffeine, Theophylline	
Antiepileptics	Carbamazepine, Phenobarbital, Phenytoin, Rufinamide Carbamazepine, Phenobarbital, Phenytoin (high), Rufinamide	value of monitoring: low Newly diagnosed epilepsy receiving monotherapy can be optimally treated without need for monitoring serum AED drug levels(10,11).
Psychiatric drug	Lithium carbonate(bipolar disorder) Valproic acid , some antidepressants (Amitriptyline , Doxepin, Imipramine)	For lithium carbonate after achieving stable therapy concentration it should be maintained at least every 3 to 6 months. value of monitoring : high(10,11). value of monitoring of Valproic acid : low.

Applying Clinical Pharmacokinetics in TDM:

1.What practitioner controls and does not control in TDM:



Pharmacokinetic factors influencing serum drug concentration and pharmacological response

f = bioavailability

Cl = clearance

Css = steady-state serum drug concentration

D = dose frequency of administration of dose.

Only the amount and method of drug delivery are under the practitioner's direct control.

To account for the patients pharmacokinetics and pharmacodynamics factors, these variables may be changed. Examples include bioavailability, clearance, steady-state SDC, and pharmacological response that the practitioner is unable to influence, in order to reach a defined SDC that produces a pharmacological response that is often observed within the drug generally acknowledged therapeutic SDC range(7).

2. The concept of therapeutic range:

Therapeutic range refers to the range of blood plasma or serum concentrations at which the intended therapeutic effect is often observed. This does not imply that patients will not benefit from concentrations below the minimal threshold or incur detrimental effects if they remain within the range. Therapeutic drug monitoring may be used to maintain a patient's medication levels within a certain therapeutic range (TDM) (12). TDM involves measuring drug concentrations, often in the blood, and comparing the findings to a preset range of serum values that are believed to reflect the medicine's optimal effectiveness and safety. Because TDM is invasive and will inform crucial clinical choices, treatment target ranges must be suitable. Patients may not obtain the full benefit of the medicine or may encounter unnecessary adverse effects if these conditions are not met. The therapeutic range of a medicine should be defined by clinical effectiveness and safety data of the highest quality (1).

3.The concept of population pharmacokinetic values:

Population pharmacokinetics is the evaluation of data from every individual in a population at the same time using a nonlinear mixed-effects model. This type of pharmacokinetics research is referred to as the study of pharmacokinetics at the population level. The nonlinear connection that exists between the dependent variable (such as concentration) and the model's independent variables and parameter variables is referred to as "nonlinear," and the word "nonlinear" is used to characterize this relationship (s). The phrase "mixed effects" refers to the parameterization, whereas "fixed effects" and "random effect" describe parameters that are the same for all individuals or variables, respectively. Data, a structural model, a statistical model, covariate models, and modeling software are the five primary components that go into the making of a population pharmacokinetic model. Structural models are used to describe the typical concentration time history within the population. One of the primary goals of the majority of population pharmacokinetic modelling studies is to get an understanding of the features of a population's pharmacokinetics as well as the sources of variability that exist within a population. Other goals include discovering predictive characteristics within a particular population in order to correlate previously measured concentrations to previously delivered dosages. Population pharmacokinetics, in contrast to the examination of data from a single individual, does not require rich data (many observations per person) or regulated sampling time patterns. We have the option of using sparse data, which consists of few observations for each participant, either alone or in combination (13).

4.Timing of SDC measurements:

Instead of relying on population values, SDCs are occasionally assessed early in a course of medication, before steady state is attained, to discover patient-specific pharmacokinetic characteristics.

SDCs are usually tested at a steady-state dosing interval (Tss) to see whether they are within the therapeutic range, which is always determined during ss. Since SDCs are typically measured at steady state and referenced to values obtained at steady state, it is essential to wait at least three to four assumed half-life (t12) values (88% to 94% of reaching full steady state) after starting drug administration so that SDC will be measured during a period when steady state may be assumed for clinical purposes. (For an expected t12 of 6 hrs, wait 18 to 24 hrs after starting medication treatment to test SDC; for an expected t If the patient reaction does not change, daily SDC assessments are usually not needed after reaching an appropriate SDC. If a situation may possibly modify the patient's pharmacokinetic values. Coadministration of another potentially changing drug and physiological changes need frequent measurements (14).

If a steady-state SDC (C_{ss}) is used properly to match a patient's C_{ss} to a population or patient specific therapeutic range, it is critical to note where in the steady-state dosage interval (ss) the C_{ss} was measured in studies establishing the therapeutic range. Alternatively, the therapeutic range is the starting point the doctor uses to create regimens based on Css measured early (apparent C_{max}, ss), close to, or near to the end (apparent C_{min}, ss) of T_{ss}. (14). When a patient's C_{ss} is measured during ss at a time that differs noticeably from the time used to establish the therapeutic range (for example, measuring a patient's C_{ss} 1 hour after giving a dose on an every 12-hour schedule when the C_{ss} for the referenced therapeutic range was actually taken at the end of ss), errors in interpretation can result. For medications having a short $t_{1/2}$ compared to those with a long $t_{1/2}$, timing errors are more severe. The first scenario has a much larger C_{SS} volatility during ss than the latte (15).

Advantages of Therapeutic drug monitoring:

Therapeutic drug monitoring has certain benefits. Patients with inflammatory bowel disease, for instance, can be under therapeutic medication monitoring. Thiopurine analogs and antitumor necrosis factor medications may be used for this, and the results for people with inflammatory bowel disease may be improved. Everolimus therapeutic drug monitoring in oncology at the time of medication-drug interaction has additional benefits. The patient's plasma concentration is significantly raised by the everolimus values there. The therapeutic medication monitoring of everolimus is crucial due to the possibility of a drug interaction. The dosage should be modified based on the plasma concentrations of everolimus. Prior to starting oral chemotherapy, the clinical pharmacist's attention has shifted to assessing the possibility of medication interactions. The analysis of medicines for therapeutic drug monitoring, which is often done in serum or plasma, might be acquired through venous blood sample. The minimally intrusive nature of the finger prick, the tiny volume, and the analyte's stability are all benefits of dried blood spot sampling in the TDM. This method could provide a quick and least intrusive sampling procedure. This allows the patient to do the finger-prick procedure at home. They are not required to train to be phlebotomists. The fact that only a tiny amount is needed is one of its additional benefits. The use of TDM is crucial for discovering drug compliance issues (16).

III. Conclusion

Therapeutic drug monitoring (TDM) is a clinical procedure that involves measuring a certain medication at desired intervals. By maximizing unique dosing regimens, this is done to maintain a steady concentration in the patient's circulation. The TDM starts when the medication is first administered, and factors including weight, organ function, dose history, reaction, and age are taken into consideration in order to establish an initial dosage regimen that is suitable for the clinical situation. TDM's primary objective is to improve therapeutic outcomes for patients in a variety of clinical settings by employing the precise dosage of difficult-to-manage drugs. This may be used to determine the best dosing regimens in order to get the best result with the least amount of toxicity. Therapeutic drug monitoring, which aids in dosage individualization, is necessary for the drug effects since drug concentration might be utilized as a substitute. However, the item that has to be watched over is the carefully chosen medications for the monitoring that needs to happen.

Fees & Funding

The authors did not receive any fund from any sources.

Conflict of interest

Authors did not declare any conflict of interest.

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