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REVIEW ARTICLE

Optimizing Patient Care: A Review on Therapeutic Drug Monitoring of some Clinically used Drugs

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ABSTRACT

Therapeutic drug monitoring (TDM) is a tool for optimizing the prescription in clinical practice to perform the drug assay and interpretation the result to get the constant concentration in the patient bloodstream. TDM was started 60 years ago and the objective of TDM is to maximize the therapeutic effect of therapy by reducing toxicity and efficacy failure by monitoring patient compliance. As we already know that these drugs have a narrow therapeutic window. The scope of TDM in India has additional indications because it will help reduce the drug resistance in patients treated by antimicrobial agents and help decide the highly effective therapy for individual patients. The clinical application of TDM is very useful for pharmacoeconomic study which can be improve the patient adherence. Clinical pharmacologists could increase the utility of TDM with the expert contribution of physicians. This method can improve the individual patient therapy outcome. TDM has two important aspects to study pharmacokinetic and pharmacodynamics. TDM is very useful to decide the dose in renal and hepatic compromised patients. Patient blood profile of an individual patient plays a crucial role to get the optimum therapeutic effect with less toxicity. TDM plays a vital role in the clinical practice of antiepileptic, anti-cancer, antimicrobial, immunosuppressant therapies, and cardiac glycosides and antitubercular agents. In India, the scope of TDM will increase day by day as increase the use of investigational use of drugs and improve the utility of the clinical pharmacology department. In developing countries, TDM has a high chance to grow with high speed.

Keywords: TDM, Toxicity, Efficacy, Pharmacoeconomic, Resistance, Therapy etc.

INTRODUCTION

Most of the drug's desired and undesired effects of drugs are clinically predicted; however, certain patients show unexpected responses. Now, the concept of therapeutic drug monitoring (TDM) helps to decide the individual drug therapy to get an optimum beneficial effect and minimum toxic effect. It is done by the clinical laboratory with the help of chemical parameters after the complete medical interpretation. TDM can change any drug prescribing procedures.[1] TDM helps to decide drug dose for the person by interpretation of drug concentration in blood plasma and able to maintain the drug concentration in therapeutic drug window. A narrow therapeutic drug ranges between minimum effective concentration (MEC) and maximum safe concentration. These drugs give extraordinary relation between plasma drug concentration and therapeutic effect. Certain drugs give a non-liner relationship between the drug concentration and the therapeutic effect. TDM

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grew out of the opinion that all patients have not shown similar responses at similar doses; in higher concentrations above the maximum safety concentration (MSC), the drug can be able to give therapeutic results when the concentrations below the MEC and the drug can be ineffective.[2-4] As per the Figure 1 plasma drug concentration is effect the theraputic effect of drug. if the drug concentration between the maximum safe concentration (MSC) and minimum effective concentraion then patient get theraputic effect. In case the drug concentration is more than maximum safe concentration (MSC) drug give toxic effect.

The objective of TDM is to get individualized therapeutic regimens with optimum patient benefit.[5] TDM enables the assessment of the efficacy and safety of a particular medication with the knowledge of pharmacokinetics (PK), pharmacodynamics (PD), and pharmaceutics. TDM involves measuring drug concentrations in various biological fluids such as plasma, serum, tear, urine and interpreting the concentrations of the drug to relate for clinical purposes.

Pharmacologists and clinical pharmacists use PK principles to assess these interpretations for therapeutic drug interaction. Some incidents of severe toxicity of some drugs such as digoxin, phenytoin, lithium, and theophylline create the need for TDM concept.[3,4]

The science of TDM was introduced with a new aspect of clinical practice in the 1960s with the publication of initial PK studies with theories of mathematical. In late 1960 emerge with clinical PKs and in starting of 1970, especially focused on adverse drug reaction (ADR) and demonstrated

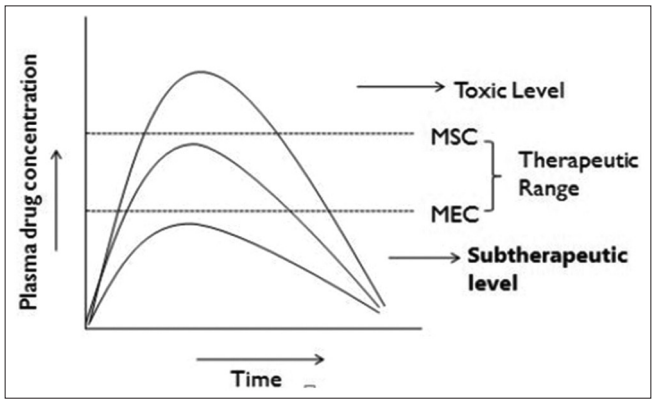

Figure 1: Drug concentration in blood with time plot

a therapeutic drug range. Many drugs have great effectiveness with high toxicity with a narrow therapeutic index (TI); such drugs require the TDM for desired clinical results with safety. TDM is also able to analyze the cost-effective analysis in health care. Very few cost-effective studies have been performed in TDM. The use of certain drugs without TDM would increase the risk of under- or overdosing, emphasis should not be placed solely on cost-effectiveness but rather on how such interventions can be applied in the most cost-effective and clinically useful manner.[1]

TDM is not suggested for all drugs because it is an expensive processer. TDM is suggested for some specific drugs when an optimum therapeutic point is not known and difficult to identify. TDM is especially done for those drugs which have a narrow therapeutic window, especially in antibiotic aminoglycoside, in bronchodilator theophylline, in anticancer drugs methotrexate, in cardiac drug digoxin, in antiepileptic phenobarbital, phenytoin, and in psychoactive lithium. TDM helps the health-care provider in dose adjustment to get optimum benefit with minimum toxicity. After the dose adjustment, health-care provider and patient complete the objective as soon as possible.[1,2]

A team of physicians, pharmacists, and nurses work together to complete the task of TDM. To get excellent results, each and every member of the team have technical skills and good communication between all the team members. Continues training and education of all the team members is compulsory. To advocate the TDM practice, more educational programs are required (Saleem *et al*., 2020).

In mid-1980s, TDM was introduced with the monitoring of a few drugs. First, it was done in a large teaching hospital later it was started in a private biochemistry department. The service of TDM was improved day by day with the passing of every year and more drugs are incorporate. However, the least number of setups is available due to a lack of funding by the government for TDM. In the current scenario, TDM's scope has expanded globally with increasing the number of drugs. Some specific drug therapies are the focus of TDM such as antimicrobial anti-tubercular drugs and antiretroviral therapy (BJCP2011).

CRITERIA TO PERFORM THE TDM

Narrow therapeutic window

The TI is the range of drug doses at which the treatment is highly effective without any adverse events. Drugs with a narrow TI have a narrow window between their effective doses and those at which they produce adverse toxic effects.

Efficacy failure

Patients are suffer from non-compliance due to the efficacy failure of some drugs. Hence, the chronically used drugs require conclusive evaluation of compliance to prevent the therapy failure.[6] TDM works like a great weapon to assure the efficacy with changing drug efficacy. In developing countries have been increasing demand for generic medicine for many years but sometime generic medicine may be of substandard quality for better quality drugs better quality control is required specially for narrow therapeutic window drugs.[7] Efficacy failure may be possible with changing the brand different brands can be given different levels of bio-availability. TDM would be helpful to understand the efficacy failure in patients after changing the brands of antiepileptics.[8]

Drug toxicity and interaction

When a drug has a narrow therapeutic window, then, the drug has a higher chance of toxicity and TDM is used as a solution to reduce the chance of toxicity and drug interaction. Nausea and vomiting may be early symptoms of digital toxicity.
As per the report of Ismail *et al*., 64.4% of patients were not found the appropriate concentration of gentamycin. In the prescription of aminoglycosides, these antibiotics can cause renal toxicity.

MAJOR DRUG CLASS WHERE TMD IS REQUIRED

Antiepileptic drugs

These drugs are offered freedom from the seizure with minimum adverse effects. As we know that TDM is a tool to get better therapeutic efficacy with minimum adverse effects. To know the various efficacy-related doubts, we use the TDM. TDM is not directly related to the antiepileptic agent efficacy but gives better seizure control with minimum side effect.[9] Antiepileptic drugs are the most common class in which TDM is performing. Phenytoin and valproic acid are antiepileptic drugs which more common for TDM. Dose adjustment to control seizures is the most common reason which can improve the patient's profile with the help of TDM.[10]

Anticancer drugs

Worldwide, cancer is the leading cause of death. Chemotherapeutic agents play an important role in the treatment of cancer.[11] Oral anticancer drugs show very high individual variability in PKs (ADME). Therefore, TDM has been used to improve the cancer treatment standard.[12] In the case study of cancer treatment, half of the patients do not achieve target plasma concentration in the first cycle of the treatment; now, to get the optimum benefit, we need to use the individual therapy deciding tool TDM.[13]
As per an Indian study, 598 cycles with a high dose of methotrexate 88.7% cycles were achieved by a single plasma monitoring of drug level at 54 h. In another report, similar results were obtained in 42 h of monitoring.[14,15]

Antimicrobial agents

Antimicrobial agents can kill or inhibit the growth of microorganisms in relation to PK and PD. In this, we can expose the relation the PK relation with minimum inhibitory concentration (MIC). All the antimicrobial agents have different PK/PD values. The therapeutic effect of the drugs can be understood on the basis of the maximum drug concentration (C max) to MIC ratio in relation of time.[16]
Aminoglycoside: Aminoglycoside toxicity is directly related to the concentration in blood, and the objective of TDM is to achieve the concentrations between the MEC and MSC to get the optimum benefit of any therapy. To reduce the incidence of toxic effects,

TDM use like a great tool. As we all know that antibiotics class of aminoglycosides has a narrow TI. TDM of aminoglycoside has meaning to decide the individual therapy monitoring. Aminoglycosides cause serious toxicity like nephrotoxicity and ototoxicity when the concentration is more than the maximum safe concentration. This type of incidence is possible with aminoglycosides because it have narrow therapeutic Window. For the clinical application the Aminoglycosides therapeutic range given in Table 1.

Several patients are suffering from renal impairment. If the dose of aminoglycosides is not adjusted, toxicities such as nephrotoxicity and ototoxicity are seen due to the reduction of aminoglycosides clearance, for example, in the burn patients, renal clearance is increased so the dose of aminoglycosides given in high dose with reducing the dose frequency.[17,18]

Beta-lactam antibiotics (for example, penicillin, cephalosporin)

TDM is less common for these drugs, as they are typically dosed at standardized levels.

Beta-Lactam's TDM has not been performed due to the wide TI. However, beta-lactum PK variability may be vast. However, TDM may be measured in several cases, like the patient is renal compromised or with severe infections. In most conditions, bacteria will regrow very rapidly when the concentration of beta-lactam falls from the MIC.[19-23]

Glycopeptide antibiotics (for example, vancomycin)

TDM is standard for vancomycin because of its narrow therapeutic range and potential for nephrotoxicity and ototoxicity.

Therapeutic levels are very commonly observed to maintain therapeutic efficacy and to reduce the level of toxicity. Vancomycin is a very common antibiotic which is require TDM and very commonly performed globally. Region for vancomycin antibiotic monitoring is methicillin-resistant staphylococcus aureus and guidelines for the recommended dosing.[24] An AUC_{0-24}/MIC ratio >400 was able to improve clinical outcomes and also correlated with more rapid abolition of the bacteria.[25] In clinical practice, AUC_{0-24} is not performed regularly.[26]

Immunosuppressants

In several autoimmune diseases, allergies, and transplant-related surgery, immunosuppressants are used in very huge amount.[27] Especially, kidney transplant surgery cases are increasing day by day. A transplant recipient requires immunosuppressant's during his/her whole life. Three types of immunosuppressant are used: (i) calcineurin inhibitors (CNIs): Tacrolimus or cyclosporine, (ii) antimetabolite: Mycophenolate mofetil, and (iii) corticosteroids. CNIs are work as the backbone of immunosuppressive regimens in kidney transplants in the present days.[27] The immunosuppressant has a narrow TI and TDM is required because of variable PKs for individuals. In the transplant recipient, sub-therapeutic and supra-therapeutic drug concentration can worsen the result of transplant.

As per the report of Klara, the patients through the use of immunosuppressants after kidney transplantation and liver transplantation were often found to be the targeted result.[28] TDM of immunosuppressants is widely processed in Indian clinical practice, especially for the patients of post-transplant, and several Indian studies have been available as the same.[29,30]

METHODS USED FOR DRUG ASSAY

There are several ways to perform the TDM

i. High-performance liquid chromatography (HPLC)
ii. Liquid chromatogram mass spectroscopy (LC-MS)
iii. Fluorescence polarization and
iv. Enzyme-mediated immunoassay techniques are the most commonly used techniques for performing TDM in India, with HPLC and LC-MS being commonly used techniques.[4,7,31]

IS TDM HELP GET MAXIMUM THERAPEUTIC BENEFIT?

There is no conclusive data which demonstrate a reduction in the rate of mortality from TDM. However, the study of Lent Ever *et al*. demonstrates the reduction in the cost by reduction in the hospital

Table 1: Show different classes of drugs with its therapeutic range

Class	Drugs	Therapeutic range
Antiepileptics	Phenytoin	43–101 µg/mL
	Valproate	10–20 µg/mL
	Carbamazepine	4–11 µg/mL
	Phenobarbitone	12–30 µg/mL
	Oxcarbazepine	3–36 µg/mL
	Ethosuximide	39–99 µg/mL
Aminoglycosides	Amikacin	20–35 µg/mL
	Tobramycin	4–8 µg/mL
	Tobramycin	4–8 µg/mL
Cardiac glycosides	Digoxin	0.8–2 ng/mL
Calcineurin inhibitors	Cyclosporine	100–400 ng/mL
	Tacrolimus	7.0–20.0 ng/mL
Antimetabolites	Methotrexate	<1 µmol/L

Table 2: Show priority level for therapeutic drug monitoring for different drugs

Priority Level	Treatment condition	Drugs
High priority	Non-critically ill patients	Lithium, phenytoin, amikacin, and gentamicin.
Moderate priority	Co-treatments	Methotrexate, vancomycin, and cyclosporin
Low priority	Clinical assessment	Digoxin, valproate, phenobarbital and carbamazepine

stay and minimizes the toxicity.[32] However, a clear relation between the exposure and efficacy of several drugs has been easily understanding and always favored to get the maximum therapeutic benefits of therapy.

THE WHO PRIORITY LEVEL FOR TDM CONSIDERING THE CONVENTIONAL INDICATIONS

The WHO in 2019 prepared the list of drugs [Table 2] for TDM in the list of essential *in vitro* diagnostic tests and prepared a list of drugs to be monitored on a priority basis. They were classified into the following categories.[33]

PERFORMANCE OF TDM IN INDIA

Serum drug concentration monitoring is one of the most consistently used techniques for optimum therapeutic benefit. However, in developing countries, most of the used drugs are not processed for TDM.[5] TDM is a multibillion-dollar market and it is dominated by developed countries like the United States but in a recent survey, 55% of TDM services are available in Asia (South-East) and India works like a leader in this region.[34] In India, TDM is processed by clinical pharmacology unit and biochemistry unit. Still, India after 50 years of TDM history, there is no central registry. Clinical pharmacologists have done complete monitoring including drug assay and clinical interpretation. He is also give the suggestion about dose adjustment, patient compliance, unresponsiveness to therapy, ADR, drug interaction, and decide the drug dose in different pathological and physiological conditions. In the laboratories, complete teamwork for TDM in which a clinical pharmacologist shows a vital impact with, a pharmacist, medical officer, nurse, and laboratory scientist. On the other hand, the clinical biochemistry laboratories work for drug assays and they did not provide further clinical interpretation.[7] In the past 20 years, both clinical pharmacology and biochemistry laboratories are increased.

CONCLUSION

TDM has facilitated to individualize drug therapy for patients and help start with personalized therapy for an individual patient. TDM is a chance for clinical pharmacologists to reduce the therapeutic challenges and work as a vital part of a health-care team.

The scope of TDM is increased as compared to the past two decades ago and used as a vital tool to minimize toxicity with maximum therapeutic benefit. If TDM is implemented in India, it used as a crucial tool to decide the individual drug therapy for antiepileptic and cancer patients. TDM can be used as a great weapon to fight against antimicrobial resistance and is very helpful to decide the dose of immunosuppressants in transplant surgery such as liver and kidney transplants.

TDM also demonstrates the reduction in the cost of treatment by reducing the hospital stay and helping to decide the individual therapy as soon as possible for the maximum therapeutic benefit.

REFERENCES

1. Touw DJ, Neef C, Thomson AH, Vinks AA. Cost-effectiveness of therapeutic drug monitoring: A systematic review. Ther Drug Monit 2005;27:10-7.
2. Tange SM, Grey VL, Senécal PE. Therapeutic drug monitoring in pediatrics: A need for improvement. J Clin Pharmacol 1994;34:200-14.
3. 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;80:516-9.
4. Atkinson AJ Jr., Nordstrom K. The challenge of in-hospital medication use: An opportunity for clinical pharmacology. Clin Pharmacol Ther 1996;60:363-7.
5. Kang JS, Lee MH. Overview of therapeutic drug monitoring. Korean J Intern Med 2009;24:1-10.
6. Krasowski MD. Therapeutic drug monitoring of the newer anti-epilepsy medications. Pharmaceuticals (Basel) 2010;3:1909-35.
7. Gogtay NJ, Kshirsagar NA, Dalvi SS. Therapeutic drug monitoring in a developing country: An overview. Br J Clin Pharmacol 2001;52(S1):103S-8.
8. Greenberg RG, Melloni C, Wu H, Gonzalez D, Ku L, Hill KD, *et al*. Therapeutic index estimation of antiepileptic drugs: A systematic literature review approach. Clin Neuropharmacol 2016;39:232-40.
9. Al-Roubaie Z, Guadagno E, Ramanakumar AV, Khan AQ, Myers KA. Clinical utility of therapeutic drug monitoring of antiepileptic drugs: Systematic review. Neurol Clin Pract 2020;10:344-55.
10. Harivenkatesh N, Haribalaji N, David DC, Kumar CM. Therapeutic drug monitoring of antiepileptic drugs in a tertiary care hospital in India. Clin Neuropharmacol 2015;38:1-5.
11. Kumar N, Kumar R, Nemaysh V, Lal N, Luthra PM. Bis ((1, 4-dimethyl-9 H-carbazol-3-yl) methyl) amine-mediated anticancer effect triggered by sequence-specific cleavage of DNA leading to programmed cell death in the human U87 cell line. RSC Adv 2016;6:67925-40.
12. Groenland SL, van Eerden RA, Verheijen RB, Koolen SL, Moes DJ, Desar IM, *et al*. Therapeutic drug monitoring of oral anticancer drugs: The Dutch pharmacology oncology group-therapeutic drug monitoring protocol for a prospective study. Ther Drug Monit 2019;41:561-7.
13. Rebollo J, Valenzuela B, Duart-Duart M, Escudero-Ortiz V, Gonzalez MS, Brugarolas A. Use of therapeutic drug monitoring of cancer chemotherapy to modify initial per-protocol doses. J Clin Oncol 2010;28:e13015.
14. Dhingra H, Kalra M, Mahajan A. Safe administration of high-dose methotrexate with minimal drug level monitoring: Experience from a center in North India. Pediatr Blood Cancer 2020;67:e28394.
15. Kapoor G, Sinha R, Abedin S. Experience with high dose methotrexate therapy in childhood acute lymphoblastic leukemia in a tertiary care cancer centre of a developing country. Pediatr Blood Cancer 2012;59:448-53.
16. Mouton JW, Dudley MN, Cars O, Derendorf H, Drusano GL. Standardization of pharmacokinetic/pharmacodynamic (PK/PD) terminology for anti-infective drugs: An update. J Antimicrob Chemother 2005;55:601-7.
17. Roberts JA, Lipman J. Antibacterial dosing in intensive care: Pharmacokinetics, degree of disease and pharmacodynamics of sepsis. Clin Pharmacokinet 2006;45:755-73.
18. Udy AA, Roberts JA, Boots RJ, Paterson DL, Lipman J. Augmented renal clearance: Implications for antibacterial dosing in the critically ill. Clin Pharmacokinet 2010; 49:1-16.
19. Bakker-Woudenberg IA, Roosendaal R. Impact of dosage schedule of antibiotics on the treatment of serious infections. Intensive Care Med 1990;16:S229-34.
20. Craig W. Pharmacokinetic and experimental data on beta-lactam antibiotics in the treatment of patients. Eur J Clin Microbiol 1984;3:575-8.
21. Mouton JW, Vinks AA, Punt NC. Pharmacokinetic-pharmacodynamic modeling of activity of ceftazidime during continuous and intermittent infusion. Antimicrob Agents Chemother 1997;41:733-8.
22. Vogelman B, Gudmundsson S, Leggett J, Turnidge J, Ebert S, Craig WA. Correlation of antimicrobial pharmacokinetic parameters with therapeutic efficacy in an animal model. J Infect Dis 1988;158:831-47.
23. Vogelman BS, Craig WA. Postantibiotic effects. J Antimicrob Chemother 1985;15(Suppl. A):37-46.
24. Martin JH, Norris R, Barras M, Roberts J, Morris R, Doogue M, *et al*. Therapeutic monitoring of vancomycin in adult patients: A consensus review of the American society of health-system pharmacists, the infectious diseases society of America, and the society of infectious diseases pharmacists. Clin Biochem Rev 2010;31:21-4.
25. Rybak M, Lomaestro B, Rotschafer JC, Moellering R Jr., Craig W, Billeter M, *et al*. Therapeutic monitoring of vancomycin in adult patients: A consensus review of the American society of health-system pharmacists, the infectious diseases society of America, and the society of infectious diseases pharmacists. Am J Health Syst Pharm 2009;66:82-98.
26. Jeffres MN, Isakow W, Doherty JA, McKinnon PS, Ritchie DJ, Micek ST, *et al*. Predictors of mortality for methicillin-resistant *Staphylococcus aureus* health-care-associated pneumonia: Specific evaluation of vancomycin pharmacokinetic indices. Chest 2006;130:947-55.
27. Lallana C, Fadul CE. Toxicities of immunosuppressive treatment of autoimmune neurologic diseases. Curr Neuropharmacol 2011;9:468-77.
28. Heim-Duthoy KL. Renal transplantation. In: Dipiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, editors. Pharmacotherapy: A Pathophysiologic Approach. 5th ed. New York: McGraw Medical Publishing Division; 2002. p. 852-4.
29. Tiwari P. Therapeutic drug monitoring of immunosuppressants: An overview. Indian J Pharmacol

2007;39:66-70.
30. Manvizhi S, Mathew BS, Fleming DH, Basu G, John GT. Combined approach with therapeutic drug monitoring and pharmacogenomics in renal transplant recipients. Indian J Nephrol 2013;23:71-3.
31. Bansal SB. Therapeutic drug monitoring of tacrolimus in kidney transplantation. Indian J Transplant 2020;14:8.
32. Van Lent-Evers NA, Mathôt RA, Geus WP, van Hout BA, Vinks AA. Impact of goal-oriented and model-based clinical pharmacokinetic dosing of aminoglycosides on clinical outcome: A cost-effectiveness analysis. Ther Drug Monit 1999;21:63-73.
33. Advani M, Seetharaman R, Pawar S, Mali S, Lokhande J. Past, present and future perspectives of therapeutic drug monitoring in India. Int J Clin Pract 2021;75:e14189.
34. Tiamkao S, Towanabut S, Dhiravibulyn K, Pranboon S, Sawanyawisuth K. Is the Thailand epilepsy service adequate to help patients? Neurol Asia 2013;18:271-7.