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Research Article

Basic Concepts of Therapeutic Drug Monitoring

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ABSTRACT

Therapeutic Drug Monitoring (TDM) is the process of measuring the concentration of a drug in blood and then correlating it clinically in order to optimize the therapy for the patient. It started in the 1960s and the last three decades have seen enormous spurt in the number of hospitals and laboratories routinely doing it in order to provide greater insights into factors that determine a patient's response to drug therapy. It is done mainly for drugs with narrow margin of safety, whose therapeutic effects cannot be quantified clinically. Suitable analytical tests like High Performance Liquid Chromatography (HPLC) and Immunoassays are available to detect drug or its metabolites and the results are then interpreted in the context of the condition of the patient. It serves as a useful tool to provide tailor made optimal drug therapy to the patient, thereby maximizing the efficacy and minimizing the side effects.

Key words: TDM, drug monitoring, drug optimization, therapeutic window.

INTRODUCTION

Therapeutic drug monitoring (TDM) is a process in clinical pharmacology which specializes in measuring the concentration of certain drugs in the body fluids and clinically interpreting it to obtain useful and often life saving information. It is defined as "*the use of drug concentration measurements in body fluids as an aid to the management of drug therapy for the cure, alleviation or prevention of disease"*[1]. TDM is done only for a few selected drugs with a

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narrow therapeutic range where the challenge is to avoid both sub-therapeutic and overtly toxic dose[2].

The concept of TDM first emerged around mid 1970s in some clinical laboratories after some studies showed its potential rewards. In 1960, Buchthal showed a direct correlation between plasma concentrations of phenytoin and degree of seizure control in epilepsy patients[3]. In 1967, Baastrup and Schou demonstrated the relationship between pharmacological effects of lithium with its plasma concentration[4]. These studies, along with the emergence of clinical pharmacology as an independent branch and development of appropriate analytical methods led to a greater understanding of TDM and its potential benefits[5]. In India, TDM started in mid 1980s and the last three decades have seen tremendous growth in its scale of popularity. Currently, TDM exists in mainly two settings in India: firstly under the aegis of clinical pharmacology departments in large scale teaching hospitals (e.g. King Edward Memorial Hospital, Mumbai), and secondly in private sector where it is either done in clinical biochemistry laboratories or in a dedicated clinical pharmacological unit (CPU) of a corporate hospital (e.g. Apollo Hospital, New Delhi)[6].

Need for TDM: For most of the drugs, pharmacological response and clinical effect can be readily assessed and quantified by means of clinical parameters like blood pressure, heart rate, blood sugar, urine volume etc. But for certain drugs, like phenytoin and digoxin, therapeutic efficacy or possible toxicity cannot be accurately gauged by means of these clinical end points. Historically, for these drugs the approach of giving a minimum standard dose to each patient has been followed ("*one dose fits all*" regimen)[5]. However, with the advent of pharmacogenomics and the fact that drug metabolism may vary from one patient to other, measuring the accurate drug concentration at various time points has become essential to monitor the therapeutic response and suspect/avert any potential toxicity due to overdose or drug interactions. A routine monitoring however is not advocated for most drugs and only clinically relevant tests must be performed[7]. At present, there are about 20 therapeutic drugs which are routinely monitored[8].

Criteria for TDM: There are certain criteria laid down for an efficient TDM process and serve as useful guidelines before embarking upon the decision to monitor a drug. These are:

- Drug should have a narrow therapeutic range. The goal of TDM is to maintain serum drug concentration within a safe therapeutic range ("*therapeutic window*").
- An appropriate analytical test must exist for the analysis of drug and its active metabolites. The analytical method used should also be able to detect small amounts of drug, be relatively

unaffected by any concomitant medications and should be able to differentiate between similar structured compounds. High Performance Liquid Chromatography (HPLC) is the gold standard test for most drugs [9] but is difficult and needs skilled personnel to perform the test. Newer immunoassay techniques like Radio Immunoassay (RIA), Enzyme Immunoassay (EMIT), Fluorescence Polarization Immunoassay (FPIA) etc. have made the analysis aspect easier. Commercial kits can also be used wherever possible but these kits are not available for all the drugs that require TDM.

- Patient not showing adequate clinical response to the drug regimen despite being on an adequate dose (therapeutic failure).
- The therapeutic effect cannot be readily assessed by the observation of the clinical parameters i.e. a precise clinical end point is not available (e.g. anticonvulsants, anti arrythimics, antidepressants etc.)
- At any given dose, there exists large individual variability in steady state plasma concentration of the drug and/or its metabolites.

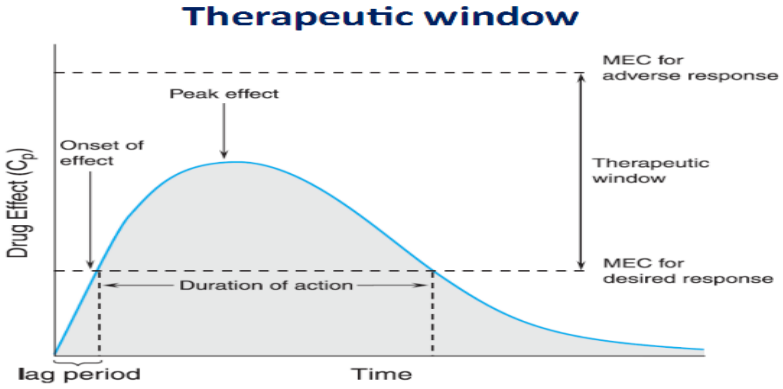

Fig. 1: It shows Therapeutic window phenomenon

Classes of drugs commonly monitored to ensure correct blood concentration include:

- Antiepileptics (Phenytoin, Valproic acid)
- Antiarrythmics (Digitalis, Lignocaine)
- Antibiotics (Gentamycin, amikacin, tobramycin)
- Antineoplastics (Methotrexate)
- Antimanics (Lithium)
- Bronchodilators (Theophylline)
- Immunosuppressives (Cyclosporine)

The TDM Process: TDM is a multidisciplinary function and requires efficient collaboration and good communication between scientists, clinicians, nurses and pharmacologists. The entire TDM process comprises of 7 steps:

- Decision to request Drug level: After an initial assessment of the scenario, a decision is undertaken. Various reasons to decide in favour of making a request are lack of expected therapeutic response, poor compliance to therapy, suspected toxicity, change in the clinical status of the patient, assessing the therapeutic efficacy after dose alteration, and to study potential drug interactions due to concomitant medications.
- Obtaining the Biological Sample: After a decision in favour of requesting drug level has been made, biological sample is collected to provide measurement. Usually serum or plasma samples are collected for this purpose. Blood sample should be collected once the drug concentration has attained a steady state (SS) (at least after 4-5 half lives at the current dosage regimen)[10,11]. This level at which SS is reached may be attained earlier for drugs given via a loading dose (e.g. digoxin). Thus, knowledge of half-life of the drug in question is helpful[12]. If toxicity is suspected, the concentration should be measured as soon as possible. Blood samples should be collected in elimination phase, usually at the end of the dosage interval. This value obtained just before the next dosing is called a "Trough value" and is useful for drugs with short half lives. Drugs with long half life can be monitored at any point in the interval between two doses[8]. For a few drugs like Cyclosporin A, whole blood should be sampled and in infants, capillary blood should be collected for TDM. Errors in the timing of sample cause maximum number of errors in interpretation of the results[13] e.g. for Lithium, a 12 hr sample post dose is most precise.
- The Request: A drug assay request is sent along with a description of the dosage regimen, patient demographics (age, sex, ethnicity etc.), indication for monitoring, detail of sample timing(s), any co-medications, and pharmacokinetic (PK) and therapeutic range of the drug in question.
- Lab Measurement: A suitable, validated and quality assured drug assay method should be performed within a clinically useful time span[14]. Verification of results should be based on the clinical context of the patient's condition and not necessarily in line with a published or established therapeutic range.
- Result communication by Laboratory: The assay results should be communicated as quickly as possible once it is verified by the senior laboratory personnel, preferably within a 24 hr period of receiving the sample[13]. Ideally, the result must reach the treating physicians before the next dose is administered to the patient. The measured drug concentrations are either reported in mass or in molar units[11]. The final result should clearly mention the therapeutic concentration range for the drug assayed.

- Clinical interpretation: Clinical interpretation of the measured drug concentration adds value to the TDM process and enables to view the results in the light of clinical context. It takes into account the individual patient demographics and the dosage regimen used. Though reference therapeutic ranges for most drugs are available, these should only be used as a guide. Also, dosage predictions can be done with the help of several softwares which can further help in individualizing the dosage regimen.
- Therapeutic management: In the light of all the information available to the treating physician, dosage regimen of the patient can be subsequently modified if required. Physicians normally accept and implement the recommendations of TDM team.

TDM Utility and Significance: TDM gives the clinicians a useful adjunct tool for providing safer and more effective, patient-centric drug therapy. It helps to maximize the efficacy of a regimen by individualizing the therapy and identifies therapeutic failure in case of non compliance or sub therapeutic dose administration. It also facilitates the adjustment of dose in case of poor therapeutic response. It can also help to identify poisoning, drug toxicity and drug abuse. A judicious TDM process can also help to distinguish a true non-responder from a non compliant patient However, for most drugs there is still lack of adequate studies depicting the cost effectiveness of TDM. In a study, Mungall *et al* (1983) showed that therapeutic drug monitoring service offered substantial benefits like fewer adverse reactions, shorter intensive care unit stay and shorter overall hospital stay[12]. Thus, the expenses incurred in TDM process are likely to be regained by positive outcomes.

TDM has its fair share of limitations as well. It is chiefly dependent on the scientific accuracy and validity of drug assays and there could be laboratory variability while reporting. The validity of suggested ranges also varies from one person to other. It is hindered by limited infrastructure and accessibility options in rural areas and the associated high costs involved. Also, there is lack of adequate training and skills in this field.

CONCLUSION

TDM is as useful adjunct tool for the clinicians as it provides them with greater insight into the factors that determine the patient's response to drug therapy. It thereby, helps to tailor the drug dose and regimen as per the clinical condition of the patient and leads to drug optimization. It should be borne in mind that TDM cannot compensate for any error in diagnosis, poor choice of drugs, errors in dispensing the medication and dosages, errors in sampling, non compliance etc. However, when used in combination with good clinical observation, it can lead to optimal

drug therapy with minimal side effects. It is a suitable candidate for positive outcomes evaluation. Thus, TDM is a useful adjunct in treating many patients provided the potential pit falls and problems are considered.

CONFLICT OF INTEREST: Nil

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