Medicon Medical Sciences
Volume 4 Issue 1 January 2023
Short Communication

Therapeutic Drug Monitoring and Its Analytical Methods - An Educational Review

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Received: December 02, 2022; **Published:** December 19, 2022

DOI: 10.55162/MCMS.04.089

Introduction

"*Concept of Therapeutic Drug Monitoring: Need of the Hour in Indian Healthcare System*".

Therapeutic drug monitoring (TDM) is defined as "the clinical laboratory measurement of a chemical parameter that, with appropriate medical interpretation, will directly influence drug prescribing procedures".It is the clinical practice of measuring specific drugs/medicines at selected intervals to maintain a constant concentration in a patient's bloodstream, thereby optimizing individualized dosage regimens. Generally, in TDM amount of drug concentration will be measured by using a suitable analytical method and the dose and therapeutic range adjusted accordingly [1].

TDM aims to improve pharmacotherapy by maximizing therapeutic efficacy and minimizing adverse events. In these instances, the blood concentration of the drug is a better predictor of the required/ desired effect(s) than the dose [2]. TDM is grounded on the principle that, for some drugs, there is a close relationship between the plasma/serum level of the drug and its clinical effect. Where such a relationship does not occur. Presently, TDM is of little value, where a clinical endpoint is either easier to measure or more reliable than the serum drug concentration assessment [3]. The fundamental procedures necessary for the quantification of the drug in the body through measuring the drug concentrations in the body fluids such as plasma and urine including recovery from body fluids, tissues, and organs, separation from the biological components, identification of the species concerned, and finally quantification [4].

Analytical methodologies employed in TDM are as follows:

1. Spectrophotometry and Fluorimetry: Prior to the advent of Gas-Liquid Chromatography (GLC) and High-Performance Liquid Chromatography (HPLC), drug samples were analysed by spectrophotometric methods.
2. HPLC and GLS: These two methods are highly specific, precise, and sensitive. Besides multiple analyses can be done. Drawbacks of these methods are i) extraction step is required ii) slow and single serial analysis, iii) column degenerates with time, and iv) multifaceted analyses require substantial processing.
3. Radio Immuno Assay (RIA): It is sensitive, and reasonably precise but involves the use of radionuclides. Cross-reactivity with other closely reacted drugs is a potential problem with this method.
4. Enzyme Immunoassays: These methods have few advantages over RIA in this no radioactive tracer is required; there is no need to separate the bound from the unbound fractions.
5. Fluorescence polarization Immunoassay (FPIA): This assay procedure combines competitive protein binding with fluorescence polarization to give direct measurement without the need for a separation procedure [4].
6. Dry chemistry.

Laboratory investigations are become a significant component of the decision of the physician, both in hospital and general medical practice. Advancing the diagnosis for physicians as well as following up and monitoring the course of the treatment, investigations in the laboratory rank highly. For the past few years due to the progress of new analytical methods, the importance of dry chemistry has continuously improved. There is fully automatic quantitative analytical equipment that has been developed for analysis and the same is used in medical science also. Additional equipment and the philosophy of centralization of investigation in the laboratory are also developed. One of the most important quarrels towards centralization is the loss of intimacy with the patient. For Example, a blood sample is drawn in a physician`s consulting room and then sent to a central laboratory depending upon timings and transport system, centralization may lead to delays in time. By that time sample may undergo certain chemical and/or biological changes. This may affect the result and leads to wrong interpretation and diagnosis. A key aspect to be observed is the time that elapsed before treatment may be investigated. In this situation sometimes dry chemistry is meant to overcome all these complications.

Dry Chemistry

Dry chemistry refers to the use of strips impregnated with dry reagents to which the specimen is added. This estimation focuses on Quantitative analysis of chemical reactions by analysers. Even though this technology is "new", clinical laboratories have been using this for the last 25 years. This technology utilizes test strips for easy identification of precise substances in the urine or blood is well established. In lieu of test strips, we now use the term 'dry chemistry.' These test strips are no longer evaluated by the human eye but by means of analysers.

The types of analysers used are Reflotron or Reflectometer, Spotchem, and Vitros. It is discernible to all working in the field of clinical chemistry that a revolution in analytical methodology has been under-way. About 30 years ago, a technician in a then-modern clinical laboratory could handle a workload of 30-50 Specimen analysers per day. Come out now is a new technology that uses dry reagent carriers for Quantitative analysis. Predominantly the mentioned devices are totally self-contained analytical elements. Where the specimens are deposited on them and that analyte activity is read directly from a measurement of change in optical properties of analysers.

The methodology used was technical information from a Survey of literature, books & data from sources. The Specimen is collected from the source. Reflotron or Reflectometer carries the evaluation and keeps track of reaction. The analyte present in the specimen in relation to the reagent in the test strip produces an acceptable reaction and the dye or color is formed which produces a certain reflectance one exposure to radiation. This facilitates Quantitative analysis comparable in precision & accuracy with classical photometry. The Reflectometer output the results in 2-3 minutes without requiring much effort. So, this technology has a more advantage whenever there is no specialized clinical pathologist and no rapid transport System [5-8].

Need for the TDM

Therapeutic drug monitoring (TDM) can be described as dose adjustment based on the measurement of drug concentration in serum, plasma, or other biological fluids in order to maintain the drug level within the therapeutic range of minimum effective concentration (MEC) and minimum toxic concentration (MTC). This might not be the exact range since some patients may respond to the concentration above and below the range, and some patients may have toxicity within the therapeutic range [5]. In a few cases, the toxic dose of medicine may be the reason for the death of the patients. This is used to individualize the dosage regimens so that drug concentrations can be maintained within a target range. Kidney and liver-impaired patients can get the maximum benefit from TDM.

The main criteria for TDM are as follows,

1. Narrow therapeutic range.
2. Pharmacokinetic variability.
3. A reasonable relationship between plasma concentrations and clinical effects.
4. Established target concentration range.
5. Availability of cost-effective drug assay.

6. When the risk of poor compliance is high.
7. When low concentration increases the risk of resistance [9, 10].

Name of the drugs required TDM [11, 12].

Sl. No	*Name of the Drug*	*Value of Monitoring*
1	Aspirin	Low
2	Amiodarone	Moderate
3	Digoxin	Moderate to High
4	Carbamazepine	High
5	Phenytoin	High
6	Lithium	High
7	Aminoglycosides	High
8	Methotrexate	High
9	Theophylline	High
10	Ciclosporin	High
11	Sirolimus	High
12	Tacrolimus	Moderate to high
13	Phenobarbital	Moderate
14	Tricyclic Antidepressants	Moderate
15	Antipsychotics	Moderate
16	Glycopeptides	Moderate
17	Antiretroviral	Low to Moderate
18	Methadone	Low
19	Morphine	Low to Moderate
20	Valproate	Low

Importance of TDM

- Measuring plasma drug concentration (PDC): Plasma drug concentration measurements alone may be helpful in several circumstances, when initiating drug therapy, the physician may find it useful to measure the plasma drug concentration and tailor the dosage to the individual. This directive applies to all drugs, although it is most important for those with narrow therapeutic ranges such as theophylline, carbamazepine, phenytoin, lithium, cyclosporine, and amino glycoside antibiotics [9].
- Monitoring in overdose: During the treatment of poisoned patients is still largely defined by the amount/quantity of poison consumption, history, clinical assessment, and laboratory parameters interpretation of ancillary investigations. Measurement of drug concentrations is clinically significant for relatively few compounds. Drug concentrations are principally important for those compounds where the concentration is predictive of serious toxicity in an otherwise asymptomatic patient such as paracetamol, lithium, digoxin, and iron [13].
- Reduce toxicity: Clinicians prescribe measurement of drug concentration levels to minimize the adverse effect of the drug, especially for the narrow therapeutic index drug (a narrow therapeutic drug in which a small amount on the higher side can cause toxic effects and lower side can cause sub-therapeutic effect). Example of drugs is digoxin, lithium; aminoglycoside antibiotics include gentamycin, tobramycin, and amikacin, phenytoin, and theophylline. Executing the daily dosage of aminoglycosides can improve patient outcomes and reduces toxicity such as ototoxicity and nephrotoxicity etc. The commendation is to check the

drug peak and trough level, but clinically trough level is recommender than the peak level [14].

- 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 an analogous structure to of parent drug. In some conditions, monitoring of serum drug levels that metabolites show false-negative results and may also apparently increase obtained plasma levels [15].
- Drug-drug interaction: Enzyme induction or inhibition leads to an increase or decrease in drug metabolism and alters drug concentrations in blood and finally affects the drug`s desired action [15].
- Precision medicine is an evolving method for disease treatment and prevention that considers individual variability in genes, environment, and lifestyle. near consequence of precision medicine, especially with the inclusion of a systems biology approach, is the selection of drugs entirely tailored to a specific patient and her or his disease. Measurement of circulating drug levels would help to describe the pharmacokinetics of these drugs in this combination, in this patient population. Measuring levels of drugs might also directly benefit the patient [16].

Importance of TDM in India

Alternative systems of medicines that are commonly used in India has 3 systems of medicines Allopathy, Ayurveda, Homeopathy, and Unani. TDM clinic identified an interaction with 'shankhapushpi' an ayurvedic preparation purported to be an anti-epileptic and memory enhancer which was given to a patient with generalized tonic-clonic seizures was well controlled with plasma phenytoin levels within the therapeutic range presented with the sudden loss of seizure control [17].

Tropical diseases Nutritional deficiencies

Diseases highly prevalent in developing countries such as infections, diarrhoea, worm infestations, TB, nutritional deficiencies, etc are serious impending problems and patients often seek late treatment. Nutritional deficiencies are often subclinical and escape detection and they have been shown to affect drug pharmacokinetics [18].

Quality of medicines and generic formulations

In developing countries, there is a constant attempt to provide drugs to most of the population at low cost and bioavailability studies are done only at the time of obtaining marketing approval. Authors have already reported from Pakistan and Vietnam that the quality of drugs used may be substandard and need additional quality control. Given that generic drugs are freely available in developing countries, quality assurance of manufacturing practice is essential. The TDM service can be used to provide an important early indication of substandard drugs.

Factors influencing conducting TDM in India are as follows,

1. Alternative systems of medicine.
2. Cost.
3. Malnutrition.
4. Difference in bioavailability.
5. Ethnic variance.
6. Lack of awareness about TDM [22-24].

Conclusion

Slight deviation from the therapeutic range of the drug alters the actions. In this situation, TDM creates vital pharmacy services which guarantee the safety and efficacy of drug use in all the diverse populations regardless of gender and age, Comorbidities like renal, hepatic, endocrine, and many disorders for the drugs with narrow therapeutic index. With recent advances in research and analytical methods in chemistry and medicines, the use of clinical pharmacokinetics helps to achieve rational drug therapy. Knowledge and skills about chemistry and analytical methods is required to perform TDM.

Funding

This article is an education review article and no funding sources.

Authors Contributions

All the authors of this article contributed equally.

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