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THERAPEUTIC DRUG MONITORING (TDM) IN CLINICAL PRACTICES: OVERVIEW

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ABSTRACT
Therapeutic drug monitoring (TDM) is a clinical practice that involves regularly measuring specific drug levels in a patient's bloodstream to maintain a consistent concentration, ensuring optimal dosage regimens. While not necessary for most medications, TDM is primarily utilized for drugs with narrow therapeutic ranges, significant pharmacokinetic variability, challenging target concentration monitoring, and those known for causing both therapeutic and adverse effects. The underlying principle of TDM relies on establishing a clear relationship between drug dose, blood or plasma drug concentration, and therapeutic effects. The process begins at the initiation of drug prescription, determining an initial dosage regimen based on factors such as clinical condition, patient characteristics (age, weight, organ function), and concurrent drug therapy. Interpretation of concentration measurements takes into account variables like sampling time relative to drug dose, dosage history, patient response, and the intended therapeutic targets. The ultimate aim of TDM is to optimize clinical outcomes by maintaining appropriate concentrations of challenging-to-manage medications for patients in diverse clinical scenarios.

KEYWORDS: TDM, Clinician, Human Genome Project, Pharmacokinetics.

INTRODUCTION
Therapeutic drug monitoring (TDM) is commonly defined as the laboratory measurement of a chemical parameter that, with appropriate medical interpretation, directly influences drug prescribing practices.[1] Alternatively, TDM involves tailoring drug dosages to maintain plasma or blood drug concentrations within a specific therapeutic range or window.[2] Drawing on knowledge from pharmaceutics, pharmacokinetics, and pharmacodynamics, TDM allows the evaluation of a medication's efficacy and safety across various clinical scenarios.[3-7] The overarching objective is to customize therapeutic regimens to maximize patient benefits. Traditionally, TDM entails measuring drug concentrations in diverse biological fluids and interpreting these values with respect to relevant clinical parameters. Clinical pharmacists and pharmacologists apply pharmacokinetic principles to analyze these interpretations. The concept of TDM gained prominence in the 1960s when initial pharmacokinetic studies established mathematical theories connecting drug concentrations to patient outcomes.[3] This era witnessed the emergence of clinical pharmacokinetics as a distinct discipline in the late 1960s and early 1970s. Pioneers in drug monitoring during the 1970s concentrated on reducing adverse drug reactions by clearly defining therapeutic ranges, leading to decreased toxicity incidents for drugs like digoxin[8], phenytoin, lithium, and theophylline.[9,10] The rise of clinical pharmacokinetic monitoring was fueled by growing awareness of drug concentration-response relationships, advancements in mapping drug pharmacokinetic characteristics, the introduction of high-throughput computerization, and improvements in analytical technology.[11] The subsequent surge in pharmacogenetic and pharmacogenomic research was catalyzed by the vast genetic data generated by the Human Genome Project (HGP). Launched in 1990, the HGP aimed to map the entire genetic instructions of the human genome, consisting of approximately 3.2 billion base pairs encoding up to 100,000 genes located on 23 pairs of chromosomes.[14] Originally projected as a 15-year project, the HGP was essentially completed by 2001.[15] Recent advancements in gene chip technology have ushered in a new era of gene-based medicinal and drug therapies.

WHICH DRUG NEEDS MONITORING ?
Narrow therapeutic window: Drug with narrow therapeutic window needs monitoring as slight variation

in the concentration can cause change in the effect of the drug.

Variation in pharmacokinetics properties: Different factor like age, gender, pregnancy, variation in the metabolising enzyme, concomitant use other drug can cause variation in the pharmacokinetic properties of a drug. Cytochrome P450 enzyme system is the major drug metabolising system. This enzyme system shows genetic polymorphism to a great extent.

Steep drug response curve: Drug with steep drug response curve binds rapidly with the receptor. So, small increase in the dose can lead to toxicity.

Plasma concentration and clinical effect: Therapeutic drug monitoring is useful if there is definite relation of the plasma concentration of the drug and its clinical effect.

PHARMACOGENETICS is a future of therapeutic drug monitoring to develop effective and safe medication. Genetic variability of the drug metabolising enzymes, drug receptor and transporter proteins cause interindividual variability in drug response. Pharmacogenetics test examines the genetic polymorphism of the drug metabolising enzymes, receptor and transporter proteins. Results of a pharmacogenetic test is lifelong and the result can be utilised for many drug where pharmacogenetic oriented therapeutic drug monitoring is important.[16]

PRINCIPLES OF TDM IN PHARMACOLOGICAL ASPECTS

Ironically, the most crucial pharmacokinetic guideline for adjusting dosage involves factors such as drug half-life, volume of distribution, and excretion. Understanding a drug's half-life allows clinicians to predict its concentration in a patient's serum at any given time, aiding in determining therapeutic, subtherapeutic, or toxic levels. This knowledge empowers clinicians to optimize dosage timing, demonstrating their proficiency in clinical pharmacokinetics. The volume of distribution parameter is essential for calculating the desired dosage, taking into account factors like the first dose based on body weight and steady-state serum concentration.[17] Clinicians can use computer software to input these parameters and compute the correct dose, adjusting it as needed based on clinical situations, such as subtherapeutic levels and declining patient conditions. In the realm of drug monitoring services, the integration of pharmacokinetics, pharmacodynamics, and pharmaceutics ensures the enhanced effectiveness and safety of specific drugs in diverse clinical contexts.[18] Pharmacokinetic variability significantly influences dose requirements, allowing clinicians to measure drug concentrations, adjust doses, and achieve the desired therapeutic levels for safety and efficacy. Factors like consent, medication errors, and drug interactions are crucial considerations. The exclusive section focusing on the measurement of drug therapy provides drug concentration data and interpretations based on pharmacokinetic parameters. Clinician interpretation of drug concentrations aims to ensure an excellent therapeutic response for the benefit of patients[19] Clinicians commonly assess drug pharmacodynamics by monitoring physiological indicators like lipid levels, blood glucose, blood pressure, and coagulation profiles.[20] Therapeutic Drug Monitoring (TDM) relies on the assumed relationship between drug dose, blood drug concentration, and pharmacological effect. Blood drug concentration serves as a guide for clinicians to make decisions, such as discontinuing treatment when the plasma drug concentration is below the therapeutic range in a clinically stable patient.[21,22] Similarly, when the plasma drug concentration is at the upper limit without any clinical effect, increasing the dosage is unlikely to be beneficial, and the risk of toxicity is elevated, prompting the need for discontinuation and consideration of alternative treatments.[23]

Table 1: Parameters which therapeutic drug monitoring relies on.

Patients factors	Therapeutic factors
Consent	Drug dose
Lipid profile	Blood drug concentration
Blood glucose	Medication error
Blood pressure	Pharmacological effect
Coagulation profile	Drug interaction

COMMONLY MONITORED DRUGS[24]

Table 2; Showing commonly monitored drugs with classification.

ANTIEPILEPTICS	Carbamazepine, Phenobarbitone, Phenytoin, Valproic acid
ANTIARRHTHMICS	Digitoxin, Digoxin, Lidocaine, NAPA, Procainamide
ANTIBIOTICS	Gentamicin, Amikacin, Tobramycin, Vancomycin
ANTIMANICS	Lithium
ANTIDEPRESSANTS	Imipramine, Amitriptyline, Clomipramine, Trimepramine, Doxepine, Desipramin, Nortryptyline, Protryptyline
BRONCHODILATORS	Theophylline
IMMUNOSUPRESSANTS	Cyclosporine, Mycophenolic Acid, Sirolimus, Tacrolin

ANTINEOPLASTIC	Methotrexate
ANTICOAGULANTS	Warfarin
ANTIFUNGALS	Amphotericin B, Fluconazole

PLASMA DRUG CONCENTRATION AND TDM

Therapeutic Drug Monitoring (TDM) involves measuring drug concentrations in the plasma to understand and manage pharmacokinetic variability, enabling adjustment of doses for optimal therapeutic effects. While a single target concentration is often sought, the reality is that there is considerable pharmacodynamic variability at any given level. Some drugs show a better correlation between plasma/blood concentration and response than between dose and response, making concentration measurements valuable .In the context of cost pressures in healthcare, drug assay laboratories typically aim to measure therapeutic drug concentrations and relate them to established therapeutic ranges. TDM encompasses not only concentration measurement but also requires expert clinical interpretation based on pharmacokinetic principles. Clinicians routinely monitor drug effects through direct measurement of physiological indices, but for some drugs, such measures may be inadequate or unavailable. TDM operates under the assumption that a clear relationship exists between dose, drug concentration, and pharmacodynamic effects.[25] Expert interpretation of drug concentration measurements is crucial for ensuring maximum clinical benefit. Plasma drug concentration measurement can guide treatment decisions, such as discontinuing treatment when concentrations are subtherapeutic but the patient is clinically stable. However, this approach may not apply universally, as seen with certain drugs like phenytoin. Additionally, if there is no response despite a drug being within the therapeutic range, adjusting the dosage may not be beneficial, and an alternative treatment might be justified. Requests for drug concentration measurements are made to manage current medication regimens or screen for potential issues. Some procedures may be in place to assess the necessity of these requests before performing assays, ensuring the rational use of resources. While this process may be time-consuming for senior personnel, it can be cost-effective in preventing unnecessary and expensive tests that do not contribute to immediate or long-term patient management.[26]

CLINICIAN ROLE IN TDM PRACTICE

Over the last two decades, the monitoring of drug levels has become increasingly popular among clinicians, clinical pharmacists, and paramedical staff. Clinicians utilize the results to make informed decisions about the appropriate drug and dosage tailored to the patient's requirements. Therapeutic Drug Monitoring (TDM) serves as a valuable treatment guide for clinicians, enabling them to achieve effective therapeutic outcomes with minimal risk of toxicity. TDM plays a crucial role in recognizing and determining whether a blood or serum level falls within therapeutic, sub-therapeutic, or toxic ranges. This involves evaluating the serum level in conjunction with the patient's clinical response, drug profile, and medical history to assess the need for dosage adjustments.[27] To facilitate this process, clinicians submit a TDM form containing the patient's complete medical history along with blood samples to the laboratory. The laboratory then measures the drug concentration in the patient's blood or plasma. However, it's essential to emphasize that clinicians ultimately treat patients, not just serum levels.[28]

FACTORS INFLUENCING TDM

Factors are mainly blood sample timing, age-related effects, the impact of pregnancy, and lactating mothers.

Blood Sample Timing

Accurate timing of blood samples is paramount for TDM. Different drugs require specific timing for optimal results. For instance, drugs like carbamazepine and digoxin necessitate samples taken at recommended intervals after dosing to avoid inappropriate concentrations. The timing varies for different drugs, such as gentamycin, lithium, phenobarbitone, phenytoin, and theophylline.[29]

Effect of Age

The elderly population, often managing multiple health conditions simultaneously, is more prone to adverse drug reactions. Geriatric patients exhibit varying sensitivities to different drug effects, with increased sensitivity to Central Nervous System (CNS) drugs but decreased sensitivity to cardiovascular effects. Ongoing research aims to better understand the pharmacokinetics and pharmacodynamics of drugs in different age groups, allowing for more personalized dosage adjustments.[30]

Effect of Pregnancy

Prescribing therapeutic drugs during pregnancy remains a challenge due to limited information in the literature. Many newer antimicrobials exclude pregnant women from clinical trials, necessitating reliance on post-marketing surveillance data to guide prescription decisions.[31]

Effect on Lactating Mothers

Breastfeeding mothers need careful consideration, as some drugs can transfer to breast milk, potentially affecting the infant. Pharmacists play a crucial role in providing information on drug factors that limit transfer and guiding women on safe practices during breastfeeding. This knowledge helps prevent inadvertent recommendations to cease breastfeeding by less informed healthcare professionals.[30]

Drug -drug interaction

Drug -drug interaction can affect drug efficacy. Interaction of drugs occurs when two or more drugs are

being taken. It may increase or decrease the drugs effectiveness.

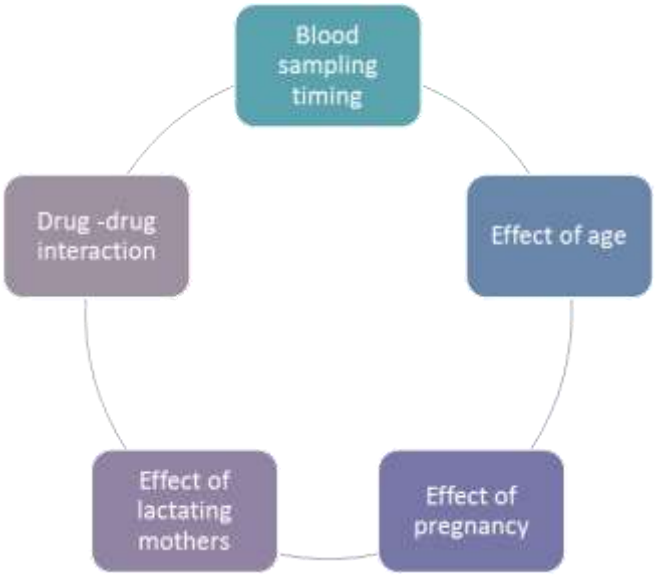

Figure 1. The aim of the review is to provide factors influencing therapeutic drug monitoring.

OPTIMIZED DOSING FOR REDUCING SELECTION OF RESISTANCE

Because of decreasing pattern of antibiotic susceptibility of pathogens which need higher antimicrobial dose to achieve a therapeutic exposure that increases treatment success.[33] Still, dosing regimens for a new drug are initially defined by targeting 'wild type' susceptible pathogens, from which are derived the so-called ecological cut-off values (ECOFF) (MIC distribution separating bacterial populations into wild type and those with acquired or mutational resistance, see for instance [(34)] or the European Committee for Antimicrobial Susceptibility Testing (EUCAST) definition of wild type bacterial isolates). If a non-wild type pathogen infects, higher doses may have to be used even if its higher MIC falls within the susceptible or in the intermediate zone. As physicians tend to exclude antibiotics associated with intermediate MICs in favour of alternative antibiotics for which the bacterial strain is still fully susceptible, potent broad spectrum antimicrobials are often used.[35] Within this context, the EUCAST and Clinical and Laboratory Standards Institute (CLSI) committees recently promoted new increased dosing regimen categories in order to help spare last resort antibiotics (EUCAST and CLSI websites for more detail). Thus, the dynamics of what the antibiotic does to the infectious bacteria in vivo has to be revised according to the MIC of the strain. EUCAST representatives suggest to integrate inherent experimental variability of MIC testing into the calculation of PK/PD targets by applying the following rules.[36] First, if the MIC is in the wild type category (susceptible organism) and lower than the ECOFF, then the ECOFF value should be used as the MIC value in the calculation of the PK/PD index. Second, if the MIC is above the ECOFF, then a ×4 MIC value should be used. Thus, stricter adherence to antimicrobial susceptibility testing (AST) guidelines will make the data generated by TDM even more clinically useful. It has to be acknowledged though that MICs represent a marker based on a single point in time and concentration. In addition, measuring an MIC is no sinecure and significant variability within and between methods exists.[37] Not everything will be solved by simple adherence to guidelines, and there is a need for further studies into optimized dosing as a consequence of regional prevalence of antibiotic resistance.[38]

CONCLUSION AND FUTURE PROSPECTS

The utilization of Therapeutic Drug Monitoring (TDM) necessitates a comprehensive approach that integrates pharmaceutical, pharmacokinetic, and pharmacodynamic techniques and analyses. A judicious application of TDM goes beyond simply measuring drug concentrations in patient blood and comparing them to target ranges. Instead, TDM serves a critical role in the creation of safe and effective therapeutic medications, allowing for the customization of treatments to individual patient needs. Moreover, TDM aids in identifying issues related to medication compliance in cases where patients may not be adhering to prescribed regimens. When interpreting drug concentration measurements, it is crucial to consider factors such as the timing of the sample in relation to the dose, the patient's dosage history, their response to the medication, and the desired clinical targets. This information guides the determination of the most suitable dosage regimen to achieve an optimal therapeutic response while minimizing the risk of toxicity. Therapeutic Drug Monitoring (TDM) proves to be highly beneficial, and studies suggest that its effectiveness can be significantly enhanced with proper guidelines. One notable challenge is the potential for drug concentrations to be sampled at inappropriate times, particularly in the inpatient setting, raising concerns

about the accuracy of TDM results. It becomes imperative for paramedics to exercise diligence in adhering to proper sample timing to optimize the quality of TDM, thereby maximizing therapeutic benefits and minimizing the risk of toxic effects. To improve the utilization of TDM, several recommended approaches can be implemented. One impactful strategy involves conducting awareness programs such as conferences, lectures, and newsletters. Additionally, multidisciplinary efforts aimed at enhancing quality can contribute to the improvement of TDM services. The incorporation of computer-based software is another noteworthy recommendation. The computerized approach holds significant promise, especially in organizations with advanced computer systems, as it minimizes human error and provides rapid and valuable information, thereby complementing and enhancing the practice of TDM. Clinicians play a pivotal role in advancing TDM services by organizing educational programs that impart knowledge to pharmacists, nurses, and clinical pharmacists. By employing the aforementioned approaches collectively, clinicians can achieve better outcomes and results in the realm of TDM.

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