DRUG DISCOVERY

Therapeutic drug monitoring: Fundamentals and optimization

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ABSTRACT

Background: Therapeutic drug monitoring (TDM) is a clinical pharmacokinetic service aimed to optimize the pharmacotherapy of certain drugs such as those with a narrow therapeutic range and complicated pharmacokinetics. It involves the determination of serum drug concentration (SDC) in samples taken at the appropriate time from the patient. Factors to consider when interpreting SDC include pharmacokinetic and pharmacodynamic drug characteristics, patient response, specific lab results and the desired therapeutic target. To be cost-effective the service should be optimized. *Area covered:* This review highlights TDM fundamentals and provides suggestions for its optimization. It covers the rationale of requesting drug level, the design of the request form, optimal sampling and analytical tools. It provides guidelines for the appropriate interpretation of drug levels. *Conclusion:* TDM should be optimized by conducting relevant research; using PK software and integrating TDM with pharmacogenomics.

Keywords: Therapeutic drug monitoring, Clinical pharmacokinetics, optimal dosing, drugs with the narrow therapeutic range

1. INTRODUCTION

Therapeutic drug monitoring (TDM) is a clinical service that aims to optimise the pharmacotherapy of drugs with a narrow therapeutic window or complicated pharmacokinetics. TDM is based on the principle of customizing dosing regimens on an individual basis. It has four components: (1) measuring serum drug concentration (SDC) in samples taken at appropriate time intervals after drug administration; (2) understanding the pharmacological profile of the administered drugs; (3) reviewing patient profiles (demographic data, clinical status, lab values, etc.) and (4) optimize the dosage regimen in individual basis (Marshall et al., 2014). These components form a framework and failure to execute any one of them will disrupt the entire service.

When used properly, TDM ensures efficacy and minimizes adverse drug events (Marshall et al., 2014). TDM reduces costs significantly while also increasing the quality of healthcare. It typically shortens the duration of hospitalization and eliminates the cost of management of adverse drug events (Dasgupta, 2012). It allows clinicians to make optimal decisions. For example, TDM is highly recommended when using immunosuppressive medications in organ transplant patients. It allows for individualized treatment that prevents

organ rejection and reduces the incidence of adverse drug reactions (Zhang and Zhang, 2018b). Recently, TDM has been used to monitor serum levels of antiviral drugs, including remdesivir, in COVID-19 patients (Pasupuleti et al., 2021). It has also been suggested to improve the clinical outcomes of hydroxychloroquine in COVID-19 patients admitted to intensive care units (ICUs) (Tecen-Yucel et al., 2021).

Measuring drug concentrations in the blood or plasma often offers insight into the extent of exposure to the drug and the possibility of achieving the target concentration in different organs and tissues are therefore relevant to medicines with a narrow therapeutic window, for which the impacts of exposure to a particular drug are difficult to anticipate without knowing the drug level. In cases of suspected drug toxicity or therapeutic failure, TDM can provide are liable guide for individual dose modifications. TDM has allowed conducting of pharmacokinetic (PK) research that played an important role in optimizing the use of certain medications amongst special populations, such as the elderly, children and those who suffer from renal or hepatic insufficiencies. Research has also helped study drug - drug interactions and the clinical impact of genetic polymorphism of metabolizing enzymes on drug PK (Al-Nasser et al., 2016; Albers and Ozdemir, 2004; Ali et al., 2018). Few studies have explored TDM in developing countries (e.g., in South America) (2015–2020) (Antunes et al., 2021). Some studies provided an overview of TDM practices in Malaysia (Abdelrahim and Ibrahim, 2013) and Pakistan and Pakistan (Sarfaraz et al., 2016). Previous research has also addressed the application of TDM in the use of antiepileptic drugs in Egypt (Ebid et al., 2007) or mood stabilizers in Saudi Arabia (Abu-Qurain et al., 2020). According to a study in Oman, blood samples for TDM are not always taken appropriately and guidelines are not adequately followed.

The literature has shown attempts to implement TDM of aminoglycosides in South Africa; however, the results were under-utilized due to a lack of clear TDM protocols (Du Toit et al., 2019). According to the findings of a study conducted in Saudi Arabia, the majority of monitored medications in major teaching hospitals were not sampled at the appropriate time, which suggests a lack of national TDM guidelines (Almohammde et al., 2021). Based on the results of these studies, there is a gap in the information related to the optimal use and development of TDM in most developing countries. This article aims to present guidelines that will help to optimize TDM services and enhance relevant research in developing countries. TDM, like other clinical services, should be optimized to ensure the best possible outcomes for patients. The following is a roadmap to the achievement of this goal as discussed in the next paragraphs.

2. CLEAR INDICATION FOR THE DETERMINATION OF SDC

The clear indication of SDC determination includes suspected toxicity and assessment of patient compliance, amongst other factors. Common indications of TDM and a list of monitored drugs are shown in Tables 1 and 2, where examples of newer drugs that required monitoring are shown in Table 3.

Table 1 Common indications for drug monitoring (Kang and Lee, 2009)

Indication	Examples
Drugs with a narrow therapeutic index	Lithium, phenytoin, digoxin
Drugs with complex pharmacokinetics	Phenytoin
Drugs' clinical efficacy is difficult to predict	Immunosuppressant drugs, antibiotics
Impaired renal function	Digoxin, aminoglycosides
Patient non-compliance	Drugs have beentaken chronically for prophylaxis
Suspected drug overdose or toxicity	Lithium, digoxin, paracetamol
Management of drug-drug interaction	Co-administering of an enzyme inducer and cyclosporine A
Suspected therapeutic failure	Resistance to vancomycin or aminoglycosides

Table 2 List of commonly monitored drugs (Schumacher, 1995)

I. Commonly monitored drugs	
Cardio active drugs	Digoxin, Amiodarone
Antibiotics	Gentamicin, amikacin, tobramycin, vancomycin
Antiepileptic drugs	Phenytoin, phenobarbitone, valproic acid, carbamazepine (ethosuximide), clonazepam
Bronchodilators	Theophylline
Immunosuppressives	Cyclosporine, FK 506
Cancer chemotherapy	Methotrexate
Analgesic	Acetaminophen, aspirin
Antipsychotic drugs and antidepressants	Lithium, tricyclic antidepressants

Table 3 List of newer drugs that required monitoring

List of newer drugs that required monitoring		
Drug class	Name of drug	Reference
Anti-TB drugs	Isoniazid, Rifampicin	(Maze et al., 2016)
Biologics for inflammatory disease	Infliximab, Adalimumab, Vedolizumab, Ustekinumab	(Hoseyni et al., 2018; Restellini et al., 2018; Franca et al., 2019; Papamichael et al., 2019)
Immuno-modulating drugs in systemic lupus erythematosus;	Hydroxychloroquine (HCQ), Mycophenolate Mofetil (MMF)	(Mok, 2017)
Systemic antifungal agents	Flucytosine, Itraconazole, Voriconazole, and Posaconazole	(Hermans et al., 2017; John et al., 2019)
Atypical antipsychotics	Iloperidone, Asenapine, and Lurasidone	(Urban and Cubała, 2017)
Newer antiepileptics	Lamotrigine, Levetiracetam, Oxcarbazepine, Topiramate, Brivaracetam, Zonisamide, Pregabalin	(Jacob and Nair, 2016)
Antiretroviral drugs for HIV management	Raltegravir & Maraviroc	(Ikuma et al., 2016; Pau et al., 2012)
Antica3.ncer	Different Kinase Inhibitors and monoclonal antibodies.	(Verheijen et al., 2017; Imamura, 2019)
Arthritis	Infliximab	(Fobelo Lozano et al., 2019)

Design of an appropriate request form

It is essential to design a request form specific to TDM, which enables clinicians to interpret results accurately. The request form must contain all relevant information, which is summarized in Table 4.

Table 4 Essential data in the request form for drug analysis

Date, hospital ID, sample identification code, etc.
Patient demographics (e.g., age, sex & weight)
Indication for testing (e.g., toxicity, non-compliance)
Time of sampling
Time of the last dose
Dosage regimen (dose, duration, dosage form)
Other medications
Co-morbidities (e.g., renal/liver disease) 4.
Additional notes (e.g., pregnancy)

3. OPTIMAL SAMPLING

Sampling time

Typically, blood samples for drug analysis are collected when their concentrations have reached a steady state, for most drugs are achieved after 4–5 half-lives. An essential requirement for some drugs is to take the sample at a specified time after the last dose, as shown below (Ali et al., 2016; Wong et al., 2014; Burton, 2006; Zhao and Jacqz-Aigrain, 2011):

1. Peak, trough, or at specified time post-dose: Aminoglycosides (Figure 1)
2. Two hours post-dose: Cyclosporine A (good correlation with the area under the curve of drug concentration versus time (AUC) and hence efficacy (Figure 2)
3. At least 6 hours post-dose: Digoxin (avoid sampling during the distribution phase)
4. Specified timed post-dose: Acetaminophen (suspected toxicity)
5. Specified timed post-dose: Methotrexate (24, 48, 72 hours)

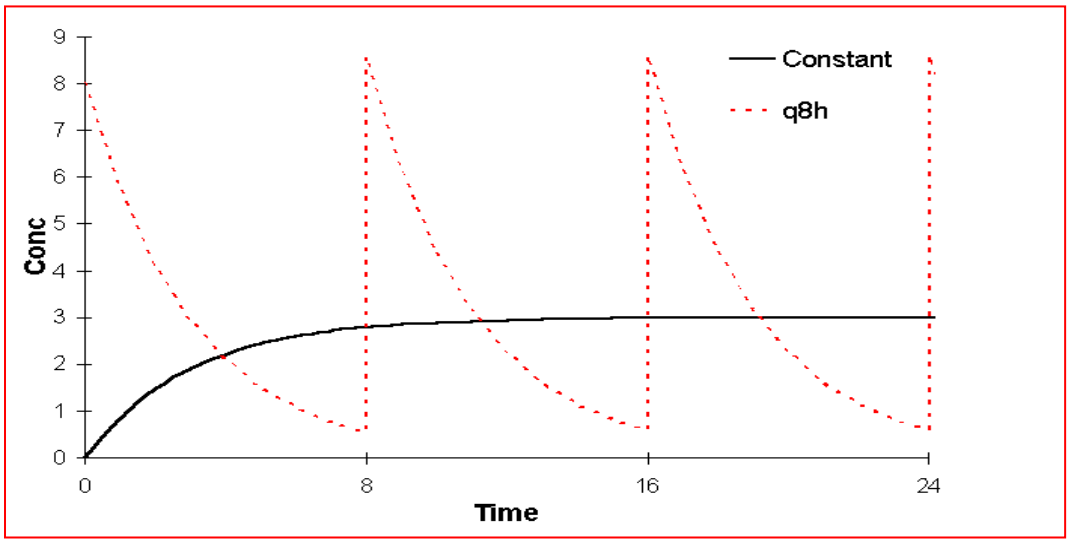

Figure 1 Peak and trough level of gentamicin (Ali et al., 2016)

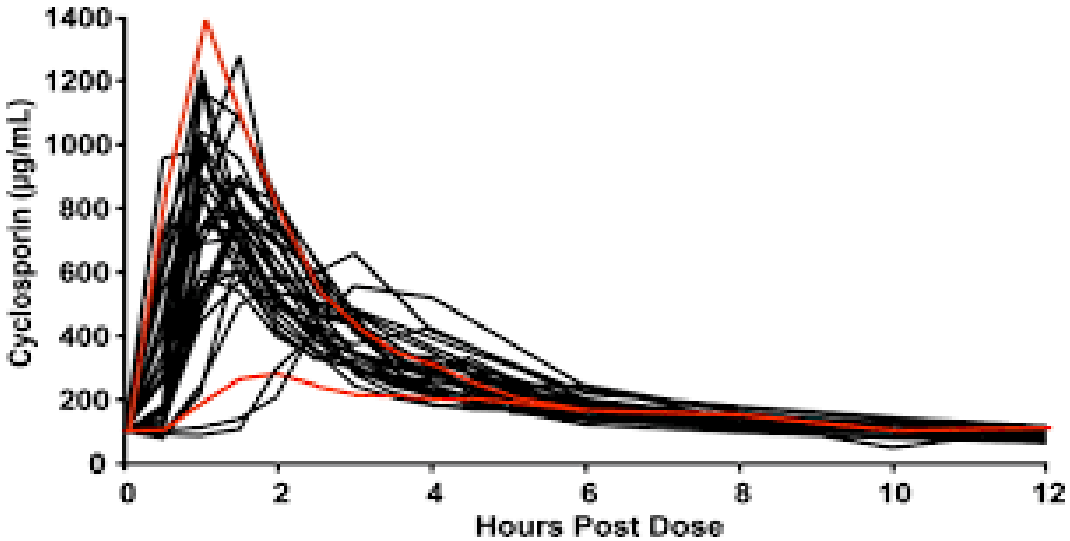

Figure 2 Variable bioavailability of cyclosporine A after oral administration (Ali et al., 2016)

The sample

Most assays for drug levels analyze serum or plasma. TDM guidelines usually recommend avoiding serum-separator tubes because these may lower drug concentrations by adsorbing drugs into the matrix. For cyclosporine A, some methods request collecting whole-blood samples. Some analytical methods are affected by the temperature of the sample (requiring standardized standardization of all variables) (Ali et al., 2016). Several studies demonstrated the use of dry blood spots for analysis of

immunosuppressants, anti- epileptic, anti-tuberculosis, anticancer and antipsychotic drugs (Capiau et al., 2019; Iacuzzi et al., 2021; Klak et al., 2019; Martial et al., 2017; Min et al., 2019; Vu et al., 2011).

Volumetric absorptive micro sampling (VAMS) was proposed as a sampling alternative for TDM and clinical trials during the COVID-19 pandemic. VAMS involves a simple sampling procedure, which can be done at home, with a minimally invasive sample volume and storage and distribution at ambient temperatures. VAMS can also absorb a fixed volume, which enhances the precision of the analysis and reduces the effect of hematocrit (Kok and Fillet, 2018).

Optimal analytical tools

Analytical methods

Methods of analysis should be rapid, to expedite the analysis of urgent samples. They should be sensitive, precise, accurate and specific and require the least possible sample size (e.g., 30 ul serum or less) specifically for the neonate. For these reasons, immunoassays such as fluorescence polarization immunoassay (FPIA), enzyme immunoassay (EMIT) and enzyme-linked immunosorbent assay (ELISA) are the most widely used procedures. It is noteworthy that HPLC-MS/MS is considered superior to immunoassays for some drugs and represents the most commonly used analytical tool for measuring drugs in dry blood spots (Dasgupta and Datta, 2008; Cui et al., 2020; Min et al., 2019; Seger and Salzmann, 2020, Tuzimski and Petruczynik, 2020; Van Nuland et al., 2020; Vogeser and Seger, 2008; Zhang and Zhang, 2018a; Zheng and Wang, 2019).

Quality control

The TDM laboratory must ensure that appropriate quality control is undertaken and laboratory personnel should be aware of the dangers of interference between drugs to be measured and similar substances, such as metabolites, endogenous compounds, or other drugs (Kang and Lee, 2009). For some drugs (e.g., cyclosporine A), the laboratory must report the method used for analysis, because the reported reference ranges depend on the analytical method (Patsalos et al., 2008; Xu and Madden, 2011).

Optimal cost

Efforts should be made to provide TDM service at a reasonable cost. The key points are to run the samples on batches whenever possible, the selection of analytical tools suitable for the workload (Ali et al., 2016) and the appropriate interpretation of drug level in context with the patient's clinical data (Nwobodo, 2014; Touw et al., 2005; Vithanachchi et al., 2021).

Appropriate interpretation of results

Variables affecting SDC

The following is a brief overview of the most critical variables that likely affect SDC (Ali et al., 2016; Aarnoutse et al., 2003; Winter et al., 2004; Ghiculescu, 2008). Active metabolites: Some monitored drugs are biotransformed into active metabolites. When evaluating the therapeutic effect of such drugs, the relative contributions of all active substances present in the serum must be considered. For example, carbamazepine is biotransformed into an active metabolite (carbamazepine 10, 11 epoxide); other examples include the psychotropic risperidone and the anticancer drug methotrexate (Hendset et al., 2006; Jacob and Nair, 2016; Karami et al., 2019).

Disease states: Some comorbidities are known to affect drug clearance (e.g., severe liver disease, renal impairment and cardiac failure), entailing consideration for TDM analysis. For instance, patients with severe renal impairment have lower albumin levels and hence higher free levels of strongly bound drugs such as phenytoin (Ghiculescu, 2008). Age: Variability in pharmacokinetic (PK) parameters (e.g., reduced renal elimination) and clinical response to drugs occurs at extremes of age. Neonates show a higher volume of distribution of aminoglycoside and longer half-life compared to infants and older children; they also show an altered metabolism of theophylline. Neonates subjected to birth asphyxia show a marked reduction in phenobarbital clearance. Among the elderly, the ability of their kidneys to excrete drugs decreases with age (Ghiculescu, 2008).

Pregnancy: Pregnant women who suffer from epilepsy and are treated with phenytoin suffer from more frequent epileptic seizures, which may be due to the activation of liver enzymes due to pregnancy itself. Moreover, pregnant women have a higher volume of distribution of hydrophilic drugs. It follows that to obtain an effective concentration of aminoglycosides, pregnant women may need higher doses compared to non-pregnant women of the same age and weight (Feghali et al., 2015). Miscellaneous variables: Variables that alter the pharmacokinetic properties of drugs and consequently blood levels include smoking, stress, environmental factors, circadian effects and drug formulation factors (e.g., drug-drug or drug-food interactions) (Mayor, 2017).

A practical guide for interpretation of SDC

It is well known that the mere measurement of drug volume in the blood without explanation is of little use and may even be misleading. Therefore, the results should be interpreted considering clinical observations of the patient's condition. The following are some relevant practical key requirements for interpreting results correctly.

Reviewing all relevant clinical and lab results and diagnoses

Examples are shown in Tables 5 and 6 (Ali et al., 2016; Ghiculescu, 2008).

Table 5 Example of important investigations and clinical observations (Kang and Lee, 2009)

Investigation	Comment
Skin, hair, gum, eye	Signs of adverse effects, e.g., antiepileptic drugs phenytoin
Culture MO, MIC	Design an optimal regimen to ensure proper selection of the antibiotic
Forced expiratory volume in one second (FEV1); peak expiratory flow rate (PEFR), arterial blood gas (ABG)	Markers for the efficacy of bronchodilators (theophylline)
ECG abnormality, nausea, vomiting, headache	Digoxin toxicity

Table 6 Examples of important biochemical and haematological parameters (Kang and Lee, 2009)

Biochemical/ haematological parameter	Drug	Comment
Elevated: Scr	Gentamicin, Vancomycin	Toxicity or reduced elimination
AST	Valproic acid, Acetaminophen	Marker for liver toxicity
Low K	Digoxin	Enhance cardiac toxicity of digoxin
CBC: progressive low RBC	Carbamazepine	Marker for aplastic anaemia
T3 & T4	Digoxin	Altered response in case of hypo- or hyperthyroidism

Realizing the nature of the therapeutic range of drugs

The reported therapeutic range of a particular drug represents a guide and not an absolute value (Ali et al., 2016). For example, the target peak of gentamicin depends on the severity, site of infection and patient's immune status (Krause et al., 2016). The therapeutic range of carbamazepine, when used to treat epilepsy, does not apply to its use in other diseases such as neuropathic pain (Ghiculescu, 2008). Achievement of drug concentrations within the therapeutic range does rule out drug toxicity. In this context, the presence of hypokalaemia represents a risk factor for digoxin cardiac toxicity (Grześk et al., 2018). Moreover, many adverse effects are dose-independent, such as phenytoin-induced gum hyperplasia and carbamazepine-associated aplastic anaemia (Gajjar et al., 2016).

Variables affecting the drug level at its target tissues

Many factors alter the effect of a drug concentration at the site of action (DiPiro, 2010). For example, phenytoin is strongly bound to plasma proteins. Normal therapeutic level (total concentration) may be associated with dose-related adverse effects in patients with very low albumin levels. In these situations, it is recommended to measure its unbound levels (Wu and Lim, 2013). Additionally, lower carbamazepine serum levels should be considered when used with other antiepileptic drugs (Panday et al., 2017). Finally, phenobarbital SDC of 200 umol/L (reference 40-170) may be acceptable in severe seizures in neonates (Byun et al., 2015).

Recognize abnormal results

Abnormal results are drug levels that are not expected given the dosing regimen and clinical status of the patients for example high gentamicin trough level, low vancomycin peak level and very high digoxin level (Ali et al., 2016). The most common causes of these observations are sampling time errors, wrong request (peak/ trough) and contamination of the sample during its withdrawal (IV-administered drugs). However, other reasons should be considered such as dosing errors, drug interactions and hepatic or renal dysfunction, etc.

Management of drug overdose and poisoning

Management of drug overdose and poisoning includes the estimation of the optimal dose of Fab digoxin (an antidote for digoxin), in case of severe digoxin toxicity (Hassan and Goyal, 2020) and the administration of N-acetyl cysteine in case of acetaminophen poisoning (Agrawal and Khazaeni, 2020).

Qualified TDM team

An optimal TDM service requires chemists and clinical pharmacists. An effective TDM service requires a collaborative, multidisciplinary approach. The clinical pharmacists may determine the initial dose of the drug, the phlebotomist collects the specimen, and the clinical laboratory staff perform drug assays (Almohammde et al., 2021; Kang and Lee, 2009; Clarke, 2016).

Continuing education and skills development

Continuous education programs regarding TDM are vital to make healthcare staff more aware of any updates and ensure effective implementation of service in clinical settings (Khairi et al., 2020). Computer-assisted learning and guidelines are superior to traditional teaching methods among healthcare professionals (Hussain et al., 2020). It is also recommended to include the basic principles of TDM in teaching courses for medical, nursing, and medical technology students (Ali et al., 2016).

Activating the patient's role in compliance with the dosing regimen

Patient education improves adherence to medications (Allison, 2012; Mathes et al., 2017). Patients should be educated on the importance of complying with the instructions from their healthcare providers and should be instructed and encouraged to report any side effects they may experience. They should also be informed about the frequency of their drug monitoring tests. For instance, when using immunosuppressive drugs such as cyclosporine A, it is necessary to educate the patient to assist in sampling the drug at specific time intervals post-administration (two hours).

TDM research and PK software

Research in TDM improves the utilization of services in clinical practice. Relevant research covers several aspects, including optimization of TDM in certain populations or clinical situations, e.g., preterm neonates, children and transplant patients (Ali et al., 2012; Ali et al., 2018; Islam, 2008; Al-Nasser et al., 2016). Many PK software solutions are now available to support utilizing serum drug levels to generate individualized dosing regimens (Fuchs et al., 2013; Drennan et al., 2018).

Integration of TDM and pharmacogenomics

The science of pharmacogenomics supports TDM to individualize dosing regimens, optimize drug effectiveness and improve drug safety. Determination of the SDC of the parent drugs and their metabolites, in combination with available pharmacogenetic tests, may provide the best clinical outcomes for drugs with a narrow therapeutic range (Albers and Ozdemir, 2004; de Leon, 2020; Doki, 2018; Jaquenoud Sirot et al., 2006; Owusu Obeng et al., 2014; Plesničar and Plesničar, 2014; Stieffenhofer and Hiemke, 2010). Regarding optimizing the use of Tacrolimus (FK506) in organ transplant patients, a dosage algorithm that takes into account demographic and clinical characteristics, as well as various genetic variants, could help to optimize early tacrolimus exposure (Yang et al., 2021). Therefore, genotyping of CYP3A5 is recommended before organ transplantation (Salvadori and Tsalouchos, 2020). Moreover, the presence of the HLA-A*3101 allele is associated with carbamazepine-induced hypersensitivity reactions and there is evidence supporting the cost-effectiveness of testing HLA-A*31:01 (before carbamazepine) (Plumpton et al., 2016).

4. CONCLUSION

The goal of therapeutic drug monitoring (TDM) is to improve the pharmacotherapy of specific medications, such as those with a narrow therapeutic range. It entails determining medication concentrations in blood samples taken at the specified time. This review highlights TDM service principles and makes recommendations for how they could be improved in developing countries. Establishing request forms, ensuring optimal sampling, qualified personnel; and quality control of the analysis methodologies were among the primary concerns addressed.

Informed consent

Not applicable.

Ethical approval

Not applicable.

Conflicts of interests

The authors declare that there are no conflicts of interests.

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Data and materials availability

All data associated with this study are present in the paper.

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