

Therapeutic drug monitoring in a developing nation: a clinical guide

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Summary

Therapeutic drug monitoring is aimed at using drug concentration measurements to manage a patient's medication requirement and optimise clinical outcome, particularly in respect of drugs with narrow therapeutic index. Typically, immunoassay methods of various techniques are employed with the advantage of rapid turnaround time and ease of operation. The chromatographic methods are specific and cost effective, though more demanding and require technical expertise. The most crucial aspect of any therapeutic drug monitoring service is the expert clinical interpretation of drug concentration measurements taking into consideration individual pharmacokinetic variability in drug disposition across different populations. The setting up of a therapeutic drug monitoring service requires enormous resources, both in terms of equipment and trained personnel. This poses considerable constraints in developing countries due to limited scarce resources, coupled with ignorance among health practitioners on the relevance of therapeutic drug monitoring in clinical practice. Consequently, the need for advocacy, training and encouragement of health practitioners on the usefulness of therapeutic drug monitoring in enhancing patient care and overall clinical outcome in a developing country such as Nigeria can never be over-emphasised.

Keywords

clinical guide, clinical interpretation, developing nation, drug concentration, therapeutic drug monitoring

Introduction

Therapeutic drug monitoring is defined as the measurement of a prescribed xenobiotic in serum or biological fluids in a single or multiple time point, with a view to influencing prescription and individualising dosage regimen to achieve maximal clinical efficacy and minimize adverse effects.¹ Therapeutic drug monitoring is not only concerned with measurement of a prescribed drug in biological matrix but may also involve an endogenous compound indicated for replacement therapy in a patient.¹ Therapeutic drug monitoring is useful for patient management where it is established that good correlation exists between pharmacological response and serum

drug concentration. It is also an essential tool for identification of potential drug–drug or food–drug interactions, by monitoring a patient's compliance with drug regimen. The mere assay or measurement of drug concentration without expert clinical interpretation amounts to waste of time and limited scarce resources. It is regrettable that in most centres of developing countries, therapeutic drug monitoring is still confined to clinical chemistry laboratories that merely 'measure' (assay only) rather than 'monitor' (assay and clinical interpretation).² Therapeutic drug monitoring service is a multibillion dollar global market dominated by developed countries such as United States.³ It is still poorly developed in low-income countries, particularly in Africa, in countries such as Nigeria. A survey revealed the availability of therapeutic drug monitoring services in 45.1% of responding countries in Africa, 54.6% in the Western Pacific, 55.6% in South-East Asia, 85.7% in the Eastern Mediterranean, 93.3% in Europe and 95.8% in the Americas. The use of affordable saliva-based testing for therapeutic drug monitoring of patients on highly active antiretroviral therapy (HAART) has been advocated in Uganda. Therapeutic drug monitoring of antiretroviral drugs has been adopted in several centres in South Africa to achieve maximal efficacy and minimize adverse effects. This article presents the prospects of setting up therapeutic drug monitoring service, highlighting procedures and relevance of clinical interpretation of drug concentration measurements in a developing country such as Nigeria.

Materials and methods

A comprehensive search was carried out using Medline, PubMed, Embase and Google Scholar to access relevant peer reviewed full journal articles, abstracts, books and theses from academic publishers' sites, professional bodies, preprint repositories and scholarly organisations. The keywords used for the search include clinical guide, developing nation, drug concentration and therapeutic drug monitoring.

Procedures in therapeutic drug monitoring

The main value of therapeutic drug monitoring for both clinician and patient is to ensure that concentration of a drug in the system is within the established therapeutic range. The belief that a clinician could achieve similar results by prescribing a drug based on an understanding of the drug's biochemistry and patient's clinical profile, then instituting dose adjustment based on patient's response is erroneous and militates against the value and principle of therapeutic drug monitoring.⁴ Studies have clearly demonstrated the clinical value of therapeutic drug monitoring, establishing criteria to determine drugs that could be routinely monitored.⁵ Indications for therapeutic drug monitoring as reported include: drug efficacy difficult to establish clinically, compliance concerns, change in dosage regimen, change in co-medication, suspected adverse effects, inadequate clinical response and conditions in which manifestation of disease state and toxicity are similar. It should be noted that therapeutic drug monitoring is contraindicated in the following instances: plasma concentration not predictably related to effects, toxicity not a realistic concern or functional laboratory tests can be employed to measure effects.

A standard therapeutic drug monitoring service can be commenced in a teaching hospital setting in a developing country with the availability of a HPLC (high performance liquid chromatography) machine and automated immunoassay analysers. The ideal therapeutic drug monitoring team other than the clinical pharmacologist comprises a medical officer, pharmacist, nurse and laboratory scientist who are involved in history taking, sample collection and analysis/assay. The monitoring service is carried out by a clinical pharmacologist who advises on compliance, dose adjustment, adverse drug reactions and drug-drug interactions.² The HPLC technique is generally demanding, requiring technical expertise, quite labour intensive and entails high turnaround time. However, it is cost effective and affordable as the consumables are locally and readily available. The automated immunoassay analysers require commercially available test kits based on various techniques such as PETINIA (particle enhanced turbidimetric inhibition immunoassay), EMIT (enzyme multiplied immunoassay technique), FPIA (fluorescence polarisation immunoassay), ACMIA (affinity chrome mediated immunoassay), CEDIA (chrome enzyme donor immunoassay) and direct chemiluminescence.⁶ These kits are usually not locally available, need to be imported and require stringent storage conditions, hence the increased cost. However, the main

advantages are the short turnaround time, being less labour intensive and ease of calibration/use.

The health system in a developing country such as Nigeria is unusual in the sense that the orthodox or western medicine co-exists alongside alternative systems such as traditional medicine and homeopathy. Patients in most cases would have visited these alternative medical practitioners before presenting in the clinic, and may be taking medication prescribed by physicians alongside herbal remedies. It is also remarkable to note that herbal remedies are increasingly used by patients who may not inform their physicians of the use alongside orthodox medicines. This poses serious challenge in therapeutic drug monitoring as experimental evidence suggests that these herbal medicines interact both pharmacokinetically and pharmacodynamically with western orthodox medicines.^{7,8} Disease burden in the developing world including nutritional deficiency is a major concern militating against improved standard of living with its negative consequences.⁹ Nutritional deficiencies though usually subclinical influence drug pharmacokinetics.¹⁰

Clinical interpretation of drug concentration measurements

Drug concentration measurement is only an aspect of therapeutic drug monitoring, as therapeutic ranges are not absolutes. Expert clinical interpretation of the concentration measurements is invaluable in order to derive any meaningful clinical benefit from the procedure. It is important to note that therapeutic ranges are mere recommendations based on the clinical response of a small group of patients taking the drug. Hence, it is not unusual for patients to experience therapeutic effects at levels below the established range, while others may experience toxicity while still within the established therapeutic range.⁴ The relationship between dose and resulting plasma concentration is dependent on pharmacokinetic variability. Major sources of pharmacokinetic variability include: lack of patient compliance, age (neonates, children, elderly), physiology (gender, pregnancy), drug-drug interactions and environmental influences. However, dose adjustments to maintain plasma drug concentrations within therapeutic range can greatly affect pharmacokinetic variability.¹¹

Dosage formulation affects liberation of drugs following oral administration. The use of controlled release delivery systems is essential in reducing adverse effects of a drug.¹² Individuals given the same dose may vary several folds in serum concentrations obtained due to pharmacokinetic variability of the drug as a result of first pass effect.¹³

Genetic polymorphism evidenced by marked variations in the cytochrome P450 isoenzymes affects serum drug concentration measurements. CYP1A2, CYP3A4, CYP2C9, CYP2D6 and CYP2E1 are the main cytochrome P450 isoenzymes that mediate the oxidative metabolism of drugs. The major and most predominant cytochrome P450 hepatic oxidative isoenzyme is CYP3A4.¹⁴ Pharmacogenetic polymorphisms affect the biotransformation and clinical outcome of a number of drugs. There are marked differences in the pharmacokinetic parameters in oral antidepressant drugs metabolised via the cytochrome P450 isoenzyme CYP2D6. CYP2C9 accounts for up to 10-fold difference in pharmacokinetic parameters in oral hypoglycemic agents, oral anticoagulants and non-steroidal anti-inflammatory agents. Hence, individualisation of therapy could be effectively predicated on pharmacogenetically based dosage adjustments. Pharmacogenetic tests, which are now advocated prior to prescription of specific anticancer and cardiovascular drugs, may likely become widespread as these tests become more cost effective and accessible.

Gender differences exist in response to drug treatment. Increases in distribution of hydrophilic drugs in females result from greater body fat in women and larger distribution volumes in males.¹⁵ Individual variations in drug efficacy and toxicity are dependent on gender differences in the pharmacokinetic parameters of several drugs. These gender-based differences underlie variations in the expression of hepatic microsomal enzymes involved in the metabolism of drugs. The female predominant expression of CYP3A4 accounts for sex differences in drug metabolism in humans. The temporal pattern of plasma growth hormone release by the pituitary regulates the sexually dimorphic expression of the cytochrome P450 isoenzyme system.

The main consideration in drug therapy during pregnancy is safety of the foetus. Monitoring is essential to achieve individualisation of therapy, considering challenges in drug disposition during pregnancy.¹⁶ Pharmacokinetics of drug use in pregnancy are influenced by compartmentalisation of drug in the foetus/placenta, placental transport of drug and foetal/placental drug metabolism.¹⁷

Chronic alcoholism induces the microsomal alcohol oxidising system involving CYP2E1 which is involved in the metabolism of toxic substances and plays a role in alcohol-induced liver damage.¹⁸ The activity of hepatic alcohol dehydrogenase, the major liver metabolising enzyme, is reduced by H₂-receptor antagonists used in the treatment of peptic ulcer disease.¹⁹ Low-dose alcohol consumption has been shown to increase warfarin activity due to inhibition

of warfarin metabolism by cytochrome P450²⁰, while high dose chronic alcoholism has been shown to decrease warfarin activity as evidenced by decreased international normalisation ratio (INR) due to increased warfarin metabolism.²¹ Tobacco contains substances such as nicotine, polycyclic aromatic hydrocarbons (PAHs) and N-nitrosoamines which induce certain cytochrome P450 enzymes involved in drug metabolism. There is increased metabolism of drugs in smokers leading to significant reduction in serum concentration, hence the need to receive larger doses of drugs than non-smokers to achieve similar pharmacological and clinical effects.²² Studies have also reported changes in warfarin disposition in smokers relative to non-smokers, with demonstrable increases in INR after cessation of smoking with consequent reduction in warfarin dose.^{23,24}

A number of disease conditions affect drug disposition. Liver disease causes impairment of drug clearance and depression of cytochrome P450 enzyme activities and gene expression.²⁵ Serum proteins produced in the liver to which many drugs bind are decreased in hepatic disease. Hence, there is elevated serum concentration of free or unbound drug with profound effect on drug toxicity, justifying the need for monitoring and dose adjustment in liver disease. Cholestasis leads to increased risk of toxicity due to reduced bile clearance.²⁶ There is increased risk of adverse effects due to accumulation of drugs and metabolites in circulation resulting from impaired renal function. Impairment in drug clearance which is dependent on glomerular filtration rate occurs in renal disease. Drug therapy in elderly patients even in drugs with a wide therapeutic window requires dose adjustment based on renal function.²⁷ Uremia in severe renal impairment results to diminution of serum binding proteins, with implication of increment in free drug concentration of strongly bound drugs with consequent increase in drug toxicity.

Congestive heart failure results in diminished tissue perfusion, reduced clearance and decrease in volume of distribution (V_d). Higher plasma drug concentrations occur in congestive heart failure due to decrease in volume of distribution and clearance resulting from impaired metabolism, thereby requiring monitoring due to increased risk of toxicity.²⁸

Thyroid function has been shown to influence the metabolism of a number of drugs. Hypothyroidism inhibits the cytochrome P450 microsomal enzyme system leading to increased serum drug levels with high risk of toxicity, while hyperthyroidism causes its activation leading to significantly low serum drug levels and reduced risk of toxicity.^{29,30} Hypothyroidism results to remarkable elongation in the half-life of antipyrine, which is appreciably

shortened during hyperthyroidism. Higher doses than usual of digitalis are required in hyperthyroid than hypothyroid patients, due to altered disposition of digitalis in thyroid dysfunction. There is no alteration in disposition of propylthiouracil during thyrotoxicosis. However, there is a reduction in plasma half-life of methimazole during thyrotoxicosis, which is observed to be elevated during hypothyroidism. Reduction in serum level of free thyroxine (T₄), associated with decreased cytochrome P450-mediated hydroxylation of phenytoin, results in increased phenytoin toxicity. Immunosuppressant therapy in organ transplantation is affected by thyroid function. Hypothyroidism results to decreased metabolism of cyclosporine leading to elevation in plasma levels and consequent toxicity.

Conclusion

Therapeutic drug monitoring service in a developing nation such as Nigeria remains poorly developed. This may be largely attributed not only to constraints posed by limited scarce resources but also ignorance among health practitioners. There is, therefore, urgent need for advocacy and proper enlightenment of the health practitioners and managers on the relevance of therapeutic drug monitoring in enhancing patient care and overall clinical outcome. Full fledged clinical pharmacology departments should be established across teaching hospitals in Nigeria, well equipped to offer therapeutic drug monitoring service. Deans of medical schools should be encouraged to incorporate teaching the basics of therapeutic drug monitoring in the curriculum. The principle and practice of therapeutic drug monitoring should be emphasised in the continuing medical education lecture series periodically organised to update health practitioners.

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