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Full Length Research Paper

Therapeutic drug monitoring: An overview of commonly monitored drugs

Nwobodo Ndubuisi N

Department of Pharmacology and Therapeutics, Faculty of Clinical Medicine, Ebonyi State University, Abakaliki, Nigeria.
E-mail: nnwobodo@yahoo.com

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Therapeutic drug monitoring is relevant in individualizing drug therapy, optimizing clinical response and reducing incidence of adverse effects. The use of many effective drugs in clinical practice is limited due to narrow therapeutic window, necessitating individualization of treatment within the framework of therapeutic drug monitoring. Therapeutic drug monitoring is an effective tool for quality assurance in clinical practice, more so for optimizing therapy. Drugs for which therapeutic drug monitoring is indicated constitute only a fraction of drugs in current use. There are clear indications and specific characteristics of drugs for which therapeutic drug monitoring may be required, most especially drugs with very low therapeutic index such as anticonvulsants, cardioactive drugs, antineoplastic drugs, antiasthmatic drugs, immunosuppressants, antidepressant drugs, antibiotics, antiretroviral drugs and antimycobacterial drugs. Hence, the goal of an ideal therapeutic drug monitoring service can be readily achieved by ensuring cautious selection of appropriate drugs and techniques that are cost-effective, highly sensitive/specific and guarantees clinical benefits to the patient.

Key words: Adverse drug reaction, clinical practice, common, drug therapy, overview, therapeutic drug monitoring, therapeutic index.

INTRODUCTION

Therapeutic drug monitoring (TDM) has been shown to be quite effective in reducing adverse drug reactions and results in significant cost saving (Ried et al., 1990; Levine et al., 1981). Therapeutic drug monitoring entails the measurement of drug concentration in serum or biological fluids in a single or multiple time point, with a view to individualizing dosage regimen to minimize side effects and enhance desired clinical outcome (Watson et al., 1997). Therapeutic drug monitoring is relevant in ensuring quality assurance in clinical practice particularly in respect of drugs with narrow therapeutic index. Recent technological development opens new opportunities for improved clinical interpretation of single drug concentration measurements and novel applications (Eliasson et al., 2013). The variability in drug exposure caused by genetic differences can be readily corrected by therapeutic drug monitoring. Drugs for which pharmacokinetic or pharmacodynamic monitoring is not indicated will be prime targets for genotype-based dosing (van Gelder et al., 2013).

The characteristics of a drug for which therapeutic drug monitoring may be useful and indicated are as follows:

- Drug exhibits narrow therapeutic window in which the dose that produces beneficial clinical effect is near dose that is likely to result in adverse effect, that is drug has low therapeutic index.
- There is no predictable dose response relationship such that a given dose that produces beneficial effect in one individual may produce adverse effect on another.
- Drug concentration in plasma cannot be predicted from dose alone due to variability in plasma levels.
- The efficacy and toxicity of a drug both correlate with serum concentration and a better correlation exists between unbound or free drug concentration than total drug concentration.
- Dose adjustment cannot be predicated on any clearly defined clinical parameter and beneficial or adverse effects of drug are difficult to monitor.
- Severe toxicity may likely occur leading to irreversible
- organ damage or death.

The following classes of drugs qualify for routine therapeutic drug monitoring: anticonvulsants, cardioactive drugs, antineoplastic drugs, antiasthmatic drugs, immuno

suppressants, antidepressant drugs, antibiotics, antiretroviral drugs and antimycobacterial drugs (Dasgupta, 2008).

MATERIALS AND METHODS

A detailed online search was done using PubMed and Goggle Scholar to access peer reviewed abstracts, comments, full journal articles and books relevant to the subject matter. The key words employed in the search were as follows: clinical practice, common, drugs, overview and therapeutic drug monitoring.

Monitoring of Anticonvulsants

Anticonvulsants are generally indicated for management of epilepsy, though may be indicated for other conditions such as cardiac dysrhythmia, migraine headache, tic douloureux and myotonia. Commonly monitored anticonvulsants include carbamazepine, phenytoin, ethosuximide, primidone, phenobarbital and valproic acid. However, other anticonvulsants such as clonazepam and sulthiame do not require monitoring (Eadie, 2001). The commonest indication for TDM of anticonvulsants is non-response to a standard dose of medication. Other indications include suspected drug toxicity, dose adjustment in pregnancy, drug interactions and to determine cause of relapse. Majority of epileptic patients achieve therapeutic control and good seizure control with appropriate dosage adjustment (Karande et al., 1992). A study has shown wide iner-individual variation in the steady state levels with anticonvulsant use in children (Singh et al., 1987). Another study highlighted the need for greater TDM referral in children stressing that 92% of them required dosage adjustment to achieve optimal concentration (Karande et al., 1995).

Monitoring of Cardioactive Drugs

Cardioactive drugs commonly monitored include digoxin, quinidine, disopyramide, lidocaine, procainamide, mexiletine and tocainide. Digoxin is the most frequently monitored drug. Immunoassay technique employed in monitoring digoxin concentration is subject to interference from cross-reactants such as digoxin-like immune reactive factor (DLIF) and steroids. Blood samples for digoxin measurement are taken 8 hours after the last dose for determination of therapeutic range, in a patient with normal renal function who has achieved steady state concentration. Drugs with significant interaction with digoxin include phenytoin, phenobarbital, heparin, cholestyramine, rifampin and quinidine. However, the most profound and potentially dangerous interaction occurs with quinidine. Quinidine is strongly bound to α_1-acid glycoprotein and variations in free fractions reported in pathological conditions.

The fluctuation of serum concentration of α_1-acid glycoprotein accounts for the extreme variability in plasma protein binding of disopyramide, which is stereoselective (Lima et al., 1990). Hence, monitoring of free fraction of disopyramide is recommended (Echizen et al., 1987). Lidocaine is also bound to α_1–acid glycoprotein, thus free fraction of lidocaine may vary significantly in disease condition.

The combined effect of procainamide and its metabolite N-acetyl procainamide (NAPA) increases the risk of toxicity which is further worsened by impaired renal function (Lima et al., 1979; Kim et al., 1990).

Monitoring of Antineoplastic Drugs

Commonly monitored antineoplastic drugs include methotrexate, cisplatin and 5-fluorouracil. Methotrexate is monitored using immunoassay technique. It is indicated for treatment of acute lymphoblastic leukaemia, Burkitts lymphoma, breast carcinoma, lung caranoma, brain tumors, osteogenic sarcoma and refractory rheumatoid arthritis. It should be noted that although nephrotoxicity is common with high dose, it may also occur at low dose therapy of methotrexate (Izzedina et al., 2005). About 30–70% of drug is protein bound, albumin being the major binding protein (Endo et al., 1996). Therapeutic drug monitoring is recommended and modification of dose to achieve between 700–1000µmol/L is advisable (Zelcer et al., 2005). Cisplatin exhibits high variability between individual patients and dosage based on body surface area. Cisplatin has been shown to impair bioavailability of phenytoin and TDM of cisplatin using total platinum measurement in plasma has been described (Sylvester et al., 1984; Salas et al., 2006).

5-Fluorouracil indicated for treatment of solid tumors is the recommended therapy for colorectal cancer. Better response rate of 5-fluorouracil is associated with improved survival rates and tolerability can be derived from individual dosage adjustment based on TDM. The clinical response and toxicity are related to area under the curve (AUC) of 5-fluorouracil which can be predicted by limited sampling strategy using two plasma concentrations (Gusella et al., 2002).

Monitoring of Antiasthmatic Drugs

Theophylline is a commonly monitored bronchodilator effective in the treatment of asthma by relaxing smooth muscles of bronchi. This drug has highly variable inter-individual pharmacokinetics and therefore, a good candidate for therapeutic drug monitoring. Immunoassay technique is commonly employed and measurement carried out after attaining steady state trough levels.

Table 1. Classes of Therapeutic Drugs Routinely Monitored in Clinical Practice.

Class of Drug	*Commonly Monitored*	*Less Frequently Monitored*
Anticonvulsants	Phenytoin[a], carbamazepine[a]	Diazepam, clonazepam
	Valproic acid[a], phenobarbital[a]	Felbamate, methsuximide
	Primidone[a], ethosuximide[a]	Gabapentin, zonisamide
	Lamotrigine	
Cardioactive	Digoxin[a], quinidine[a]	Flecainide, verapamil
	Disopyramide[a], lidocaine[a]	Mexiletine, tocainide
	Procainamide[a], NAPA[a]	Propanol, amiodarone
Antiasthmatic	Theophylline[a], caffeine[a]	
Immunosuppressants	Cyclosporine[a], tacrolimus[a]	Sirolimus, Everolimus
	Mycophenolic acid[a]	
Antidepressants	Amitriptyline, nortriptyline	Fluoxetine/norfluoxetine
	Doxepin, imipramine	Paroxetine, sertraline
	Desipramine, clomipramine	Haloperidol
	Trimipramine, lithium[b]	
Antibiotic	Amikacin[a], gentamicin[a]	Ciprofloxacin, cefazolin
	Tobramycin[a], vancomycin[a]	Chloramphenicol, nafcillin
Antiviral		Indinavir, nelfinavir
		Ritonavir, saquinavir
		Delavirdine, nevirapine
Antineoplastic	Methotrexate[a] cisplatin	Doxorubicin, tamoxifen
		Cyclophosphamide,
		5-fluorouracil
Analgesic	Acetaminophen[a], salicylate[a]	Ibuprofen, pentobarbital

[a] Immunoassay commercially available.
[b] Automated assay commercially available.

[Adapted from-Dasgupta A, Editor; (2008). Introduction to therapeutic drug monitoring. In: Handbook of Drug Monitoring Methods-Therapeutics and Drugs of Abuse. Totowa, New Jersey: Humana Press Inc; pp1-39].

Metabolism of theophylline is altered in disease condition. Theophylline is slowly metabolized in patients with severe obstructive airway disease and pneumonia (Vozeh et al., 1978). Theophylline is converted to caffeine in children. Maturation of theophylline clearance and disappearance of serum caffeine concentration are related to the demethylation pathway.

Monitoring of Immunosuppressant Drugs

Therapeutic drug monitoring of immunosuppressant drugs, which has become an integral part of transplant protocols, has contributed immensely to successful outcomes in organ transplantation. Immunosuppressant drugs are routinely monitored in transplant patients where they are employed for life-long maintenance therapy to prevent graft rejection and risk of toxicity. The most routinely used and commonly monitored immunosuppressants include cyclosporine, everolimus, sirolimus, tacrolimus and mycophenolate mofetil. Cyclosporine, a cyclic polypeptide immunosuppressant which is useful in preventing graft rejection has been shown to be effective in the long term survival of patients who have undergone solid organ transplantation (Winters, 1994). There are different assay systems for monitoring cyclosporine; although immunoassays are most frequently used, HPLC-UV still remains the gold standard for cyclosporine monitoring (Johnston et al., 2003; Holt et al., 2001). The risk of chronic graft rejection following cyclosporine therapy is directly correlated with intra-patient variability in AUC [area under the curve] values (Johnston et al., 2006; Durmont et al., 2000). Sirolimus is a macrocyclic lactone derived from the *Streptomyces hygroscopicus* (an actinomycete) with oral bioavailability of about 15% (Johnston et al., 2003). The relatively long half life of approximately 60 hours reduces the need for frequent monitoring compared to other drugs in the same category (MacDonald et al., 2000). Everolimus differs in pharmacokinetic properties from sirolimus being faster in attaining steady state concentration due to shorter half-life (Watson et al., 1996).

It is a chemically-related analogue of sirolimus with remarkable immunosuppressive property. Tacrolimus is known to have similar pharmacokinetic and pharmacodynamic profile as cyclosporine. It has emerged as an important therapeutic alternative to cyclosporine in solid organ transplantation. Whole blood is the main sample used for assaying tacrolimus, as it is highly bound to erythrocytes, hence blood concentration is markedly higher than concurrent serum or plasma concentration (Venkataramanan et al., 1995; Bauer, 2001; Jusko et al., 1995). Mycophenolate mofetil is a prodrug converted to its active metabolite mycophenolic acid shown to be effective immunosuppressant in reducing the rate of acute rejection in kidney, heart and liver transplants (Shaw et al., 2001). It has gained relevance as basic component of long term immunosuppressive therapy. The most reliable predictor of risk for acute graft rejection in the course of mycophenolate mofetil therapy is AUC (Shaw et al., 2002). Hence, dose adjustments in the course of mycophenolate mofetil therapy cannot be reliably predicted by trough plasma concentration monitoring of mycophenolic acid (Kuypers et al., 2003).

Monitoring of Antidepressant Drugs

Therapeutic drug monitoring is indicated for antidepressants particularly the tricyclic antidepressants because of their narrow therapeutic index, to enhance efficacy and reduce adverse drug reaction. Lithium is indicated for treatment of bipolar disorders (manic depressive psychosis) and commonly monitored using immunoassay method. Restriction in the use of lithium in developing countries is attributable to lack of facilities for monitoring (Shanming, 1981). Studies have indicated that high correlation exists between saliva and serum lithium levels though a particular sub-group showed better correlation (Verghese et al., 1977; Khare et al., 1983). A therapeutic range of 0.8 to 1.2mmol/L is ideal for lithium therapy and concentration greater than 3.5mmol/L considered toxic and lethal (Sashidhoran, 1982; Gadallah et al., 1988). Selective serotonin re-uptake inhibitors such as fluoxetine, sertraline, fluvoxamine, paroxetine have flat dose–response curves and wide therapeutic margin, hence monitoring is not relevant (Rasmussen and Brosen, 2000).

Monitoring of Antibiotics

Most antibiotics have wide therapeutic index and so do not require monitoring. Notwithstanding, a few with narrow therapeutic margin require monitoring to avoid toxicity, though others may still be monitored on a case by case basis (Begg et al., 2001). Aminoglycoside antibiotics employed in the treatment of life threatening microbial infections have high potential ototoxicity and nephrotoxicity at sustained elevated peak serum concentration (Black et al., 1976; Erlason and Lundgren, 1964). Elimination of aminoglycosides is relatively slow in elderly patients. This contrasts with the situation in children with high elimination rate of aminoglycosides. A disease condition known as cystic fibrosis affects the pharmacokinetics of aminoglycosides, lowering serum concentration due to rise in total body clearance and large volume of distribution (Horrevorts et al., 1988). Vancomycin, a glycopeptide antibiotic used to treat life threatening infections, is commonly restricted to treating methicillin–resistant *Staphylococcus aureus* and ampicillin-resistant enterococcal infections. Therapeutic drug monitoring is indicated due to its low therapeutic index associated with high risk of nephrotoxicity and ototoxicity. However, unlike the aminoglycosides, vancomycin pharmacokinetics are not altered by cystic fibrosis (Duffull and Begg, 1994).

Monitoring of Antiretroviral Drugs

The main classes of drugs currently in use for treatment of HIV/AIDS include: nucleoside reverse transcriptase inhibitors such as (abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, zalcitabine, zidovudine), non-nucleoside reverse transcriptase inhibitors such as delavirdine, efavirenz, nevirapine), protease inhibitors such as (amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir, ritonavir, saquinavir, tipranavir) and fusion inhibitors such as enfuvirtide (formerly T-20) and peptide T. However, accumulated evidence suggests that only non-nucleoside reverse transcriptase inhibitors and protease inhibitors satisfy the requirements for monitoring (Dasgupta and Okhuysen, 2001; Gerber, 2000). Most anti-retroviral drugs show narrow therapeutic index with range of toxicities including pancreatitis, nephrolithiasis and neurologic complications (Gatti et al., 1999). Immunoassay techniques do not have a place in the monitoring of antiretroviral drugs. Tandem mass spectrometry and high performance liquid chromatography (HPLC) methods are routinely employed. Mass spectrometry is preferable, far more sensitive and specific than HPLC technique which is quite labour intensive, requires large sample volume, lengthy sample preparation steps and technical expertise (Moyer et al., 1999).

Monitoring of Antimycobacterial Drugs

Tuberculosis is caused by an aerobic acid-fast bacillus known as *Mycobacterium tuberculosis* that thrives in parts of the body such as lung, kidney, bone and spine; with relatively high oxygen tension. There are five first-line drugs used in the treatment of tuberculosis including isoniazid, rifampin, pyrazinamide, ethambutol and strep-

tomycin. Administration of rifampin-isoniazid combination therapy for nine months results in cure rate of 95-98% in susceptible strains. Therapeutic drug monitoring in the management of tuberculosis is useful in allowing timely adjustments in drug therapy particularly in patients with multiple drug resistant tuberculosis, concomitant HIV infection or other co-morbidities. It is also essential in sorting out drug-drug interactions; in combination with clinical and laboratory data serves as useful tool in the management of complicated tuberculosis (Peloquin, 2002). A study reported that though underutilized, therapeutic drug monitoring is quite useful in the treatment of active tuberculosis associated with HIV infection in which drug concentrations are below acceptable levels (Babalik et al., 2011). Therapeutic drug monitoring of antimycobacterial drugs ensures that serum concentrations above the minimum inhibitory concentration (MIC) is maintained to achieve better clinical results (Peloquin, 1997).

CONCLUSION

A number of drugs are commonly monitored with a view to enhancing quality assurance in clinical practice by ensuring that drug concentration is within the expected therapeutic range. A number of criteria are employed in selecting which drug qualifies as potential candidate for therapeutic drug monitoring, most importantly in respect of drugs with narrow therapeutic index. Hence, the main goal of therapeutic drug monitoring service is to ensure accurate clinical interpretation of drug concentration measurements with a view to influencing dose adjustment. This can be achieved by cautious selection of appropriate drugs and techniques suitable for therapeutic drug monitoring with a view to enhancing cost-effectiveness, rapid turnaround time, high sensitivity/specificity and considerable therapeutic benefits to the patient.

CONFLICTS OF INTEREST

I hereby declare that there are no conflicts of interest whatsoever.

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