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Review article

REVIEW ON THERAPEUTIC DRUG MONITORING

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ABSTRACT

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 .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, immunosuppressant, antidepressant drugs, antibiotics, antiretroviral drugs and antimycobacterial drugs. Antipsychotic 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: TDM Reference Values and Therapeutic Window, Practical Aspects of TDM, Adverse drug reaction,, therapeutic drug monitoring, and 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 concentrations 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.

MATERIALS AND METHODS:

A detailed online search was done using Goggle Scholar to access peer reviewed abstracts, comments, full journal articles and books relevant to the subject matter. The aim of the guidelines is to optimize the use of TDM of psychotropic drugs, including mainly antidepressants, antipsychotics, and opioid substituents, and to recommend when TDM and genotyping/phenotyping procedures may help to improve pharmacotherapy. Therefore, the indications for TDM, taking into account the different classes of drugs, had to be defined, the most relevant reports of the literature had to be selected, especially also with regard to reference values of plasma concentrations (therapeutic windows) and steady-state drug concentrations at clinically relevant doses. There was also a general need for recommendations regarding the practice of TDM in the clinical context and in the laboratory.

Table 1. Classes of Therapeutic Drugs Routinely Monitored in Clinical Practice[18].

Class of Drug	*Commonly Monitored*	*Less Frequently Monitored*
Anticonvulsants	Phenytoin[a], carbamazepine[a] Valproic acid[a], phenobarbital[a] Primidone[a], ethosuximide[a] Lamotrigine	Diazepam, clonazepam Felbamate, methsuximide Gabapentin, zonisamide
Cardioactive	Digoxin[a], quinidine[a] Disopyramide[a], lidocaine[a] Procainamide[a], NAPA[a]	Flecainide, verapamil Mexiletine, tocainide Propanol, amiodarone
Antiasthmatic	Theophylline[a], caffeine[a]	
Immunosuppressants	Cyclosporine[a], tacrolimus[a] Mycophenolic acid[a]	Sirolimus, Everolimus
Antidepressants	Amitriptyline, nortriptyline Doxepin, imipramine Desipramine, clomipramine Trimipramine, lithium[b]	Fluoxetine/norfluoxetine Paroxetine, sertraline Haloperidol
Antibiotic	Amikacin[a], gentamicin[a] Tobramycin[a], vancomycin[a]	Ciprofloxacin, cefazolin 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.

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GLOBAL INDICATIONS FOR TDM OF A DRUG OR GROUP OF DRUGS:

Global indications for TDM include the following:

• Plasma concentrations are highly variable at a given dose (high pharmacokinetic variability)

• A therapeutic range of plasma concentrations has been established with a narrow therapeutic index (including latent toxicity), or a steep plasma concentration–therapeutic effect relationship was found

• Problems in the prediction of clinical effects and problems in dose titration

• Long-term treatment

TABLE 2. Indications for TDM of Drugs with Respect to Individual Therapeutic Situations That are Often Encountered in the Clinical Setting

- Suspected noncompliance
- Lack of clinical response or insufficient response even if doses are considered adequate Drugs, for which TDM is mandatory for safety reasons (eg, lithium)
- Adverse effects despite the use of generally recommended doses
- Suspected drug interactions
- Patients with pharmacokinetically relevant comorbidities (hepatic or renal insufficiency, cardiovascular disease)
- Combination treatment with a drug known for its interaction potential in situations of comorbidities, “augmentation,” etc
- Presence of a genetic particularity concerning the drug metabolism genetic deficiency, gene multiplication)
- Problems occurring after switching from an original preparation to a generic form (and vice versa)
- Relapse prevention in long-term treatments, prophylactic treatments
- Recurrence despite good compliance and adequate doses Children and adolescents , Elderly patients (>65 y)

Table 2 gives a summary of the indications for TDM of Psychotropic drugs in frequently encountered clinical situations. Except for “suspicion of non-compliance,” the validity

Of most of the other indications had to be examined separately For each drug category. Certainly, TDM should be requested Only when required clinically and when there is a chance

that The result will provide an answer to the relevant questions. There is consensus to propose 5 levels of recommendation:
1. Standard of care: Established therapeutic window.
2. Recommended: Putative therapeutic window obtained From plasma concentration measurement at therapeutically Effective doses (fixed-dose studies).
3. Probably useful: Suggested therapeutic ranges are plasma Concentrations at therapeutically effective doses obtained From steady-state pharmacokinetic studies. *Level of evidence:* Clinical data from retrospective analysis of TDM Data, single case reports, or non-systematic clinical experience.
4. Unclear: Therapeutic ranges from steady-state pharmacokinetic Studies at therapeutically effective doses. *Level of Evidence:* Valid clinical data so far lacking or inconsistent results.
5. Not recommended: Unique pharmacology of the drug,
eg, irreversible blockade of an enzyme or flexible dosing according to clinical symptoms.
For all levels of recommendation, TDM is indicated in case of suspicion of non-compliance. Non-compliance seems to occur at a highly underestimated frequency and should therefore be tested for whenever suspicion is justified, eg, after nonresponse or only partial response. A recent study revealed that during a 3-month treatment with SSRIs, 72.5% of the patients missed at least 1 dosing day, and 29% of the patients had dosing lapses of 2 or more days.[6]

TDM REFERENCE VALUES AND THERAPEUTIC WINDOW:

Most often, data are available in the literature on steadystate plasma concentrations of a psychotropic drug and its main active metabolite, which were obtained from studies with volunteers or selected patients who were treated with a fixed dose of the drug for a given period of time. However, clinical ratings (efficacy, adverse effects) were rarely carried out. These plasma concentration measurements may be considered helpful in clinical situations in which the clinician needs to know whether the patient is compliant, or whether his drug metabolism shows some particularity. Studies on the plasma concentration–clinical effectiveness (efficacy, adverse effects) relationship are not available for all drugs.[7] They are needed to obtain reliable therapeutic plasma concentration ranges (therapeutic windows), but the quality of the studies varies widely if carried out at all (cf levels of recommendation with respect to TDM).
TDM is well established for tricyclic antidepressants, but the evidence for a significant relationship between drug concentration and therapeutic outcome of new antidepressants is poor.[8, 9] Except for testing of compliance, the TDM of antipsychotic drugs is less mandatory than that of tricyclic antidepressants. However, for some antipsychotics such as clozapine and olanzapine, there is fair evidence for a therapeutic window. It is increasingly accepted that TDM is indicated in patients treated with methadone or *R*-methadone.[10]

PRACTICAL ASPECTS OF TDM:

Recommendations for the Laboratory

The laboratories should carry out the assays in compliance with good laboratory practice (GLP). They need to be validated for linearity, selectivity, accuracy, precision, recovery, and sensitivity [limits of detection (LOD) and quantification (LOQ)]. The laboratory should carry out internal quality control and participate in an external quality assurance program.
The concentrations of the psychoactive drug and its metabolite(s) should be reported with the reference concentrations range, in either mass or molar units (SI, International System of Units). The LOD should be indicated in situations where concentrations are too low to be reported. It

would be an advantage for a laboratory to offer an interpretation and clinical pharmacologic advice provided with each report. However, the number of laboratories that can offer expert interpretation is probably small because of structural reasons. It is therefore recommended that the treating physician should ask a clinical pharmacologist for advice.

Recommendations for the Treating Physician

TDM does not appear to be justified for all patients and all situations, and TDM cannot replace clinical judgment. The physician should be aware that TDM is not available for all drugs and that its benefit depends on their level of recommendation for TDM, on the availability of established plasma concentration ranges at fixed doses, and on the therapeutic window. He/she should also take into consideration the recommendations of the laboratory in regard to information on anticoagulants, the timing of blood sampling (steady-state conditions, trough levels, etc), and conditions for shipment to the laboratory before sampling blood for TDM. To ensure quality of the analysis, indications on co medications, which may interfere with the assay, may be useful. The request form should be filled out properly. Finally, the physician should be aware that laboratories differ in their presentation of results with regard to the units in which they are expressed. Many recommendations deal with the interpretation of the results and suggestions for decision making by the physician.

Use of TDM Results in the Clinic

TDM is thus one aspect of the therapeutic strategy. Its results should be interpreted with expertise, especially in situations where drug interactions, pharmacogenetics particularities, or comorbidity may influence the fate of the drug in the organism. Recommendations by the laboratory are limited by the fact that the physician possesses adequate information on the patient's clinical situation. On the other hand, junior psychiatrists should get acquainted with the interpretation of results under supervision of an expert who is trained in clinical psychopharmacology and pharmacokinetics. Admittedly, some important questions related to TDM are still waiting for an answer. Most studies on the plasma concentration– clinical effectiveness relationship were carried out with groups of patients. There is some preliminary evidence that individual patients may have their own optimal plasma drug concentration ranges, possibly because of clinical (diagnosis) or biologic (eg, individually regulated drug transport in the brain) particularities. With regard to the indications presented in Table 2, the blood collection and assay conditions developed for routine TDM may show their limits. As a rule, trough concentrations are measured, but in some situations peak concentrations would show a better correlation with adverse effects. In forensic psychiatry, when drug concentrations are either extremely high or very low, the standard calibration curve used for TDM may not be suitable.

CONCLUSION:

The usefulness of TDM to optimize pharmacotherapy recognition is the consequence of the improvement of analytic procedures and the new quality standards introduced in the laboratories, but mainly of an increased knowledge on metabolism, pharmacokinetics, and pharmacogenetics of psychotropic drugs. Pharmacokinetic interactions have important consequences on the clinical outcome, and TDM is a powerful diagnostic tool to show the underlying pharmacokinetic causes. There is clearly a need for consensus guidelines because the field of TDM has experienced a dramatic development, but the harmonization of its practice has been neglected. These guidelines developed by an interdisciplinary group will contribute to an improvement of the use of TDM by laboratory practitioners and clinicians of psychiatric patients are now recognized. ThisA numbers 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.

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