Basic Principles of Therapeutic Drug Monitoring

Ahmed S. Ali¹,*, Mahran S. Abdel-Rahman², Ab Fatah Ab Rahman³ and Osman H. Osman¹

¹Faculty of Medicine King Abdul-Aziz University, Saudi Arabia
²Faculty of Pharmacy, Taibah University Saudi Arabia
³Clinical Pharmacy Program, School of Pharmaceutical Sciences, University Sains Malaysia

Abstract: Therapeutic drug monitoring (TDM) is a tool that can guide the clinician to provide effective and safe drug therapy in the individual patient. It is a team work service; the clinical pharmacist plays an important role to guide the team. TDM involves not only measuring drug concentrations, but also the clinical interpretation of the result. This requires knowledge of the pharmacokinetics, sampling time, drug history; the patient's clinical condition and specific laboratory results. The following review summarize the criteria to insure optimal TDM service.

Keyword: Drug monitoring, Pharmacokinetics, optimal dosing.

1. INTRODUCTION

Therapeutic drug monitoring (TDM) has contributed substantially in assisting patient management and has become an important tool in clinical medicine. The provision of TDM service requires a team effort from various clinical services. In a typical TDM service, the clinician will determine the initial dose of a drug. A clinical pharmacist assists by providing essential information about the drug, revises the initial regimen if necessary, and provides a plan for TDM. A nurse or a phlebotomist collects the blood sample at an appropriate time. The nurse usually documents essential information and clinical response of the patient. Finally, a clinical laboratory scientist or chemist performs the drug assays (Figure 1). Once the assay result is available, the clinical pharmacist provides interpretation of the result and makes appropriate recommendations to the physicians. A new drug regimen will include drug dose, dosage interval, route of administration, after taking into consideration patient-specific factors such as age, weight, and renal function.

Recommendation of an appropriate drug regimen takes into account the patient's individualized pharmacokinetics and clinical condition or response. The following are important considerations to ensure an optimum TDM service in any setting [1-3]:

(1) Measurement of patient's serum or blood drug concentration (SDC) taken at appropriate time after drug administration,

(2) Knowledge of pharmacological and pharmacokinetic profiles of the administered drugs,

(3) Knowledge of relevant patient's profile like demographic data, clinical status, laboratory and other clinical investigations, and

(4) Interpretation of SDC after taking into consideration all of the above information and individualizing drug regimen according to the clinical needs of the patient.

TDM when used properly helps to improve efficacy and minimize toxicity of selected drugs especially those with narrow therapeutic ranges or with marked pharmacokinetic variability [4]. Table 1 shows drug characteristics that may require monitoring of their SDC. Commonly monitored drugs are shown in Table 2.
Figure 1: Role of health professionals in a TDM service.

Table 1: Common Drug Characteristics for TDM [5]

| Drug with an established relationship between its SDC and therapeutic response and/or toxicity |
| Drug with a narrow therapeutic index. Example: Lithium, phenytin, and digoxin |
| Drug with large individual variability at steady state SDC in any given dose |
| Drug with poor relationship between its SDC and dosage |
| Drug with saturable metabolism. Example: phenytin |
| Drug with poorly defined end point or difficult to clinically predict the response. Example: immunosuppressant drugs |
| Drug whose toxicity is difficult to distinguish from a patient's underlying disease. Example: Theophylline in patients with chronic obstructive pulmonary disease |
| Drug whose efficacy is difficult to establish clinically. Example: Phenytoin |

Table 2: Commonly Monitored Drugs [4]

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardio active drugs</td>
<td>Digoxin; (amiodarone,)</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>gentamycin, amikacin, tobramycin, vancomycin</td>
</tr>
<tr>
<td>Antiepileptic drugs</td>
<td>Phenytoin, phenobarbitone, valproic acid, carbamazepine (ethosuximide); clonazepam</td>
</tr>
<tr>
<td>Bronchodilators</td>
<td>theophylline (caffeine)</td>
</tr>
<tr>
<td>Immunosuppressant</td>
<td>Cyclosporine and FK 506</td>
</tr>
<tr>
<td>Cytotoxic drugs</td>
<td>methotrexate</td>
</tr>
<tr>
<td>Analgesic</td>
<td>Acetaminophen and aspirin</td>
</tr>
<tr>
<td>Antidepressants and antipsychotics</td>
<td>lithium and tricyclic antidepressants</td>
</tr>
</tbody>
</table>
2. OPTIMIZATION OF TDM SERVICE

With wide availability of TDM services in hospitals nowadays, there is a tendency that the service is being misused or overused. Like other clinical services, appropriate measures need to be taken to optimize its use thus, ensuring the best clinical outcomes. There are a number of criteria that need to be considered to make TDM a cost-effective service [5-7].

There are clear clinical indications for the measurement of SDC (e.g. no response to treatment; suspected non-compliance; suspected toxicity).

The specimen (i.e. blood, serum or plasma) is taken at an appropriate time and with identifiable patient information.

Appropriate analytical techniques are available to determine the SDC of the drug and/or its metabolites.

Adequate clinical information is available to allow the interpretation of SDC.

2.1. Clear Indication for the Drug Level Determination

TDM data supports the clinician to make appropriate clinical decision but it should not be used as a routine laboratory test. A rational indication of SDC determination includes assessment of patient compliance. For example, when a patient fails to respond to a usual therapeutic dose, measurement of SDC can help to distinguish between a noncompliant patient and a patient who is a true non-responder. With antibiotic therapy, TDM helps to determine whether therapy failure is due to inadequate SDC or due to bacterial resistance. TDM also provides early indicators regarding toxicity or non-reversible adverse effects before clinical symptoms are being observed. For example, progressively high trough gentamicin concentrations may provide early warning of potential renal damage. TDM can also be used to confirm a suspected drug interaction. For example, co-administration of an enzyme inducer or inhibitor is likely to affect the SDC and pharmacokinetics of cyclosporine A, thus affecting its efficacy. Patients who have impaired clearance of a drug with a narrow therapeutic index will benefit from SDC monitoring. For example, patients with renal failure have decreased clearance of digoxin and therefore are at a higher risk of toxicity. Providing TDM of digoxin in such patients will help clinicians to adjust dose regimens accordingly [8-11].

2.2. Optimal Sampling Time

Sampling After Achievement of Steady-State Condition

In most cases blood samples should not be collected until a steady-state condition has been reached. This occurs when the rate of drug administration and drug elimination are equal, for most drugs this is achieved after 4 to 5 half-lives. If a loading dose has been administered, the desired drug concentration may be achieved earlier. However, drug concentrations may be determined earlier if toxicity is suspected. It is important to wait for steady-state both at initiation and following any dosage change [1]. In certain situations, a loading dose (an initial higher dose) may be given at the beginning of a course of treatment to rapidly achieve a steady state. A loading dose is most useful for drugs that are eliminated from the body relatively slowly, i.e. have a long systemic half-life. Drugs which may be started with an initial loading dose include digoxin, and Phenytoin for acute status epilepticus [12].

Sampling at the Appropriate Time in Relation to Last Dose

When a drug is administered, it goes through the stages of absorption, distribution, metabolism and elimination. An essential requirement for some drugs is to take the sample at the appropriate specified time following the last dose [12, 13]. Errors in the timing of sampling will produce abnormal or unexpected results. Nurses and clinical pharmacists should always be aware of correct sampling times to avoid misinterpretation of results.

Accurate sampling time is critical for some drugs as shown in the following examples:

Drugs with short half lives e.g. aminoglycosides (Figure 2):

Good correlation with AUC and hence efficacy e.g. Cyclosporine A (2 hours post dose);

Avoid sampling during the distributive phase e.g. Digoxin (at least 6 hours post dose);

Specific sampling time based on a nomogram e.g. Acetaminophen toxicity (at least 4 hours post dose);

Specific sampling time e.g. Methotrexate (at various time intervals according to institutional guidelines).
2.3. Laboratory Considerations

Analytical Techniques

The analytical method should be sensitive, precise, accurate, and specific enough to measure SDC within the reference range. It should allow rapid analysis to ensure the provision of TDM service in emergency situations. In addition, the analytical technique should allow for determination of pediatric samples using the minimum possible sample size; 30 μL serum or less.

Analytical techniques vary according to different laboratory requirements and hospital budgets. Many automated chemistry instruments used for biochemical analysis have drug detection kits that can be added to their menus. Most laboratories use immunoassay methods for TDM service. One of the most popular bench-top assay instruments is the fluorescence polarization immunoassay (FPIA) by Abbot Diagnostics, commonly known as the TDx® method. Another immunoassay is the enzyme multiplied immunoassay technique (EMIT®), currently marketed by Siemens Healthcare Diagnostics. The instruments and software of these assay techniques may have undergone continuous upgrading but the principles of assay determination remain the same.

For some drugs, chromatographic techniques such as gas chromatography (GC) and high performance liquid chromatography (HPLC) may be used. Unlike immunoassays, chromatographic techniques do not depend on commercially available reagent kits. GC and HPLC are considered the gold standard for specificity, and they have the advantage of being able to simultaneously detect the parent drug and its metabolites. These techniques are more suitable for research institution and are not usually used for routine measurement in patient care settings.

The laboratory that is involved in the TDM service must ensure that appropriate quality control is undertaken. This includes having internal and external quality control programs. All quality control parameters should be documented and assessed regularly by the clinical chemist. The laboratory technologist or clinical chemist should be aware of analytical interferences and artifacts, which may lead to falsely high or low concentrations of drugs [14-17].

Different methods of analysis may give different values for a given sample due to differences in their specificities. A parent drug may cross react with its metabolites, thus giving a higher concentration value. For this reason, when an assay is requested for cyclosporine A (CSA), the clinical chemist must report the method used for analysis because the reference range of CSA depends on the method used.

Batch Versus Individual Assay Determination

In general, SDC is expensive relative to other routine biochemical analysis. Efforts should be done to provide a good service at reasonable cost. Consider performing sample assay in batches whenever possible and select an analytical tool that is most suitable to the work load.

Type of Sample

The type of sample will vary according to the specific assay. Most assays allow serum, some require plasma, and for some assays either is acceptable. Samples should be collected and centrifuged as soon as possible. Avoid serum-separator tubes because these may lower drug concentrations due to the adsorption of drug into the matrix. Some assays are specific about storage of samples. Plastic cryo-vial type tubes are acceptable for most assays. For CSA, some methods specifically require whole blood, not plasma, collected in an EDTA tube. Analytical methods may be affected by temperature and all these variables should be standardized.

2.4. Appropriate Interpretation of Results

Serum drug concentration without proper interpretation of its value could be misleading. Therefore, drug concentration determinations must
always be interpreted in the context of the clinical data. Some of the key points regarding appropriate interpretation include the following [13].

(a) **Comprehensive knowledge of variables** affecting the pharmacokinetic and pharmacodynamic characteristics of the drug being monitored.

Active metabolite: Some monitored drugs are biotransformed into compounds that are pharmacologically active. When evaluating the therapeutic effect of such drugs, the relative contributions of all active substances present in the serum must be considered *e.g.* carbamazepine is biotransformed to the active metabolite carbamazepine-10,11-epoxide.

Disease states: Acute or chronic disease alters drug clearance patterns. For example, severe liver disease impairs the clearance of most antiepileptic drugs. Congestive cardiac failure can cause elevated drug concentrations of drugs dependent on hepatic metabolism for clearance. Patient with severe renal impairment has lower albumin concentration and hence high free concentration of phenytoin.

Age: Variability in pharmacokinetic parameters and clinical response to drugs occurs at extremes of age. For example, neonates during the first week have larger volume of distribution and longer half life of aminoglycosides compared to children. They also have altered metabolic pathway of theophylline and neonates with birth asphyxia show marked reduction in Phenobarbital clearance.

Pregnancy: A number of patients report an increase in seizure frequency during pregnancy, which can be attributed to behavioral factors, physical changes, pharmacokinetic alterations of antiepileptic drugs, and natural fluctuations of seizure frequency [18]. Examples of pharmacokinetic influence include changes in phenytoin absorption or metabolism. Periodic measurement of serum phenytoin concentrations is particularly valuable in the management of a pregnant epileptic patient as a guide to an appropriate adjustment of dosage. SDC may return to pre-pregnancy values after delivery, therefore, postpartum restoration of the original dosage will probably be indicated.

Other variables: Factors like smoking, stress, drug formulation (generic versus trade name), drug-drug or drug-food interaction, environmental factors, and circadian effect can alter pharmacokinetic properties of the drug being measured.

(b) **Knowledge of relevant clinical response and laboratory investigation.** Examples of common monitoring parameters are shown in Tables 3 and 4.

### Table 3: Examples of Investigations and Clinical Observations [5]

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>skin, hair, gum, eye</td>
<td>Signs of adverse effects. (<em>e.g.</em> phenytoin)</td>
</tr>
<tr>
<td>Culture and sensitivity</td>
<td>To ensure proper selection of the antibiotic; design optimal regimen</td>
</tr>
<tr>
<td>Forced expiratory volume in one second (FEV1), Peak expiratory flow rate (PEFR), Arterial blood gas (ABG)</td>
<td>Markers for efficacy of bronchodilators (<em>e.g.</em> Theophylline)</td>
</tr>
<tr>
<td>ECG abnormality, nausea, vomiting, headache</td>
<td>Signs of adverse effects (<em>e.g.</em> digoxin toxicity)</td>
</tr>
</tbody>
</table>

### Table 4: Examples of Biochemical and Hematological Parameters [5]

<table>
<thead>
<tr>
<th>Biochemical and hematological parameter</th>
<th>Drug</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal function tests (<em>e.g.</em> SCr)</td>
<td>Aminoglycosides and Vancomycin</td>
<td>Indication of nephrotoxicity or reduced elimination</td>
</tr>
<tr>
<td>Liver function tests (<em>e.g.</em> AST, ALT)</td>
<td>Valproic acid and Acetaminophen</td>
<td>Marker for liver toxicity</td>
</tr>
<tr>
<td>Serum electrolytes (<em>e.g.</em> K⁺)</td>
<td>Digoxin</td>
<td>Enhance cardiac toxicity of digoxin</td>
</tr>
<tr>
<td>Complete blood count (<em>e.g.</em> abnormal progressive low RBC)</td>
<td>Carbamazepine</td>
<td>Marker for aplastic anemia</td>
</tr>
<tr>
<td>Thyroid function tests (<em>e.g.</em> T3 and T4)</td>
<td>Digoxin</td>
<td>Altered response in hypothyroidism or hyperthyroidism</td>
</tr>
</tbody>
</table>
C-TDM Request Form

It is essential to design a request form specific for TDM [19]. It is important the request form contains all relevant information in order to accurately interpret the results. However, it may not be possible to include every piece of information in the form. Sometimes the information can be obtained from the patient’s medical records. In addition, the clinical pharmacist/pharmacologist still has the duty to monitor and discuss patient’s clinical response with the clinician.

Dosing and sampling times must be accurately documented in the patient’s medical records and in the TDM form. It can be difficult to make sense of a result unless collection time and previous last dose is known. For example, an elevated digoxin concentration may be due to the sample being taken too early after the last dose when the drug is still in its distributive phase. It is important to note how long the person has been on the drug, to ascertain that the drug has achieved a steady-state condition. It is also useful to include on the request form any co-morbidities or other notes (e.g. pregnancy) that would assist in the interpretation of the TDM results.

Information required on TDM request form [5]

Patient demography

Name of patient-

Patient hospital number (registration number)

Ward or unit

Age, weight, height, gender, race

Smoking and alcohol consumption

Pregnancy

Gender

Relevant Clinical Summary of Patient (including indication of drug and concurrent medical problems)

Laboratory indices and concurrent drugs (including renal function tests, liver function tests, and serum electrolytes)

Information on drug requested

Name of drug requested for TDM

Dose regimen (including dose, frequency and route)

Date and time last dose given/taken

Information on sample

Sampling time

Indications for testing

To confirm suspected toxicity

To rule out non-compliance

To rule out therapeutic failure (e.g. patient not responding to treatment)

To obtain baseline value (e.g. Before pregnancy)

Other indications ....

Name of requesting clinician and signature

Date of request

2.5. Other Considerations in TDM Service

(a) Recognize the Flexible Nature of the Reference Range

Reference ranges for commonly monitored drugs are available in many TDM handbooks. They must be used as a guide rather than absolute values. The following points are provided to illustrate this fact.

The target peak of gentamicin depends on severity, site of infection, and immune status of the patient. For example, urinary tract infections can be treated with lower SDC compared to pseudomonal pneumonia.

Sometimes the reference range depends on drug indication. For example, theophylline (10 to 20 mg/L) for bronchial asthma and 5 to 10 mg/L for apnea of prematurity. Therefore, it is important to state in the TDM request form the indication of the drug.

Drug concentrations within the usual reference range do not rule out drug toxicity in a given patient. For example, physiologic variables like hypokalemia can increase the risk of digoxin toxicity.

Many adverse effects are dose-independent (or not related to SDC). For example, gum hyperplasia associated with phenytoin and aplastic anemia produced by carbamazepine.

Many factors alter the effect of a drug concentration at the site of action. For example, SDC of phenytoin...
that is within the reference range may be associated with dose-related adverse effects in patients with very low albumin level.

Consider the synergistic or additive effect of drugs. For example, a lower carbamazepine SDC may be desired when used with some other antiepileptic drugs.

In certain life threatening situations, higher than normal concentrations may be required or even recommended. For example, phenobarbital SDC of 200 umol/L (normal range 40 to 170 umol/L) may be acceptable in severe seizures in neonates provided the vital signs are normal.

(b) Recognize Abnormal Results

Abnormal or unexpected results are not uncommon in TDM. Possible causes of unusual or unexpected TDM results may arise from problems with bioavailability, drug interactions, non-compliance or medication errors. For example, unexpected high gentamicin level in a patient with normal renal function.

The most common causes of unexpected serum concentrations are

Sampling time error. This is common for antibiotics
Sample mix-up. e.g. peak/trough concentrations for gentamicin
Samples contaminated with the injected drug (e.g vancomycin) during sample withdrawal usually give very high SDC.

Other possible reasons include inappropriate dosage, generic or different brand product interchange, poor bioavailability, drug or food interactions, acute hepatic or renal dysfunction, altered protein binding and genetic factors.

(c) Knowledge of Appropriate Procedure for Management of Overdose and Toxicity

Measurement of SDC in case of overdose or toxicity requires knowledge of how the results are going to be used in management of these conditions. For example, SDC can be used to estimate appropriate dose of Fab digoxin antibody in severe digoxin toxicity. Based on the SDC obtained and an appropriate assumption of patient’s volume of distribution, the amount of digoxin in the body can be estimated. Therefore, the corresponding amount of Fab antibody can be calculated and administered. Another example is the measurement of SDC of acetaminophen in acute poisoning. The need to administer N-acetylcysteine is based on the probability of developing hepatotoxicity based on the Rumack-Matthew nomogram.

(d) Education

Continuous education program regarding TDM is important to ensure all health professionals are aware of the basic principles and to ensure effective implementation of the service in clinical setting. Strategies for physician education regarding optimal use of TDM include traditional and non-traditional education approaches [20, 21]. In general, most traditional educational approaches are effective at changing physician behavior in the short term, however, these approaches are labor-intensive and their effect has waned with time.

In view of the experiences with TDM services in Saudi Arabia, Egypt and Malaysia, we suggest to include basic principles of TDM in undergraduate courses for medical, nursing, and medical technology students as an effective tool for optimization of TDM service in developing countries. Recently, e-learning methodology (software provided as CDs) has been suggested as a tool for supporting clinicians to understand the pharmacology and pharmacokinetics relevant to drugs being monitored. This approach has been shown to be useful because most clinical professionals work in a busy environment and are often faced with restrictions due to time or other factors. E-learning, therefore, allows them pursue their studies at their own pace [21].

(e) Patient Education

Patients should be educated on the importance of complying with their physician’s orders for medications, and should be told to report any complications or side effects they may experience. Patients should also be told about the frequency of their drug monitoring tests, and why keeping their appointment is important. Patient education can increase the accuracy of sampling time. At King Abdulaziz University Hospital, patients have been provided with printed instructions.

(f) Research

Research in TDM improves the utilization of service in clinical practice. Relevant researches cover include optimization of TDM in certain population or clinical situation such as in preterm neonates, children, transplant patients and cystic fibrosis patients [22-25].
(g) Computerization of TDM Service

Computerization can simplify complex procedures and avoid errors associated with missing documentation. Guided dose algorithms can be implemented for many drugs for which TDM is required, taking into account patient-specific factors such as age, gender, weight, interacting drugs, and major organ functions. Various pharmacokinetic software are available in the market. These algorithms can also suggest monitoring of drugs at appropriate times. Computerization allows the availability of clinical data at an instant. Data such as drug regimen, dosing times, and sampling times would be available when requested. When the system is integrated with other laboratory services, the clinical pharmacist/pharmacologist can use these biochemical data to help make a decision.

3. SUMMARY

Measurement of serum drug concentration without appropriate interpretation is useless or even misleading.

Efforts should be implemented to insure cost-effective service. The following criteria are suggested:

Clear indication for the drug level determination

Insure optimal sampling time;

appropriate analytical techniques;

appropriate interpretation of results, in view of relevant biochemical and hematological parameters and clinical observations.

Reference range is considered as guide rather than an absolute value, i.e. some patients may require and tolerate higher level while others show good clinical response with lower level.

TDM specialist should be aware of appropriate procedure for management of overdose and toxicity.

Continuous education for patients and staff as well as research are also important tools to develop the TDM practice.

REFERENCES


Basic Principles of Therapeutic Drug Monitoring


Received on 15-04-2013 Accepted on 03-06-2013 Published on 30-12-2013

DOI: http://dx.doi.org/10.14205/2309-4435.2013.01.02.5

© 2013 Ali et al.; Licensee Pharma Professional Services. This is an open access article licensed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/3.0/) which permits unrestricted, non-commercial use, distribution and reproduction in any medium, provided the work is properly cited.