

Peer reviewed ORIGINAL ARTICLE

GUIDELINES TO MINIMISE HUMAN ERROR IN SOUTH AFRICAN LABORATORIES WITH REGARD TO THERAPEUTIC DRUG MONITORING

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ABSTRACT

Therapeutic drug monitoring (TDM) fulfils an important function in patient health in both the public and private healthcare systems. TDM is based on pharmacokinetic principles within the clinical laboratory and several health professionals, from different disciplines, take part in the management and implementation of the whole TDM process. Communication and collaboration between these professionals are extremely important to ensure beneficial TDM and patient care, however, human error plays a major role in the compromising of the TDM process. In this article, we discuss the most common human errors during the TDM process and give guidelines to prevent them. These guidelines must be implemented during all the TDM phases to ensure the patient receives optimal and reliable healthcare.

KEYWORDS

Therapeutic drug monitoring, communication, patient care, guidelines

INTRODUCTION

TDM refers to the individualisation of drug dosage to maintain plasma/serum or blood drug concentrations within a targeted therapeutic window^[1] and should not be confused with the testing for drug abuse. TDM is the analysis, assessment and evaluation of the circulating concentrations of drugs in the blood stream, detected in serum or plasma. TDM is especially important in drugs with a narrow therapeutic window, to detect toxicity and to test for non-compliance. These drugs include: certain cardio-active drugs, antiepileptic drugs, bronchodilators, immunosuppressants, cytotoxic drugs, analgesics, antidepressants, antipsychotics, tuberculosis drugs and antiretroviral drugs.^[2] Consequently, TDM has become standard practice in medical areas such as neurology, psychiatry, cardiology, infectious diseases and organ transplantation.^[3]

TDM forms part of a multidisciplinary health service to patients^[4] and requires team work from the physician, nurse, pharmacist, technologist and clinical pharmacokineticist (physician or clinician) to do the final clinical interpretation.^[4] The communication and collaboration between all these individuals will improve the desired outcome for the patient.^[4]

TDM optimises the patient's dosing regimen based on the drug concentration found in the patient's blood at a specified time and certain pharmacokinetic characteristics of the patient, such as clearance and the volume of distribution.^[5] The correct collection of the blood sample is equally important to aid the interpretation of the drug concentration result.^[6] The whole process starts with a clinical question (e.g. why is the patient not responding?), followed by an analytical strategy (blood level measurement) to answer the question.^[6]

Reasons for a TDM request may include the following:^[5,7]

1. Assessment of compliance with the new or current medication regimen.

2. Can the lack of appropriate therapeutic response be due to sub-therapeutic plasma concentrations?
3. Symptoms of drug toxicity.
4. Following changes in the dosage regimen and individualising the therapy.
5. Following changes in the clinical condition of the patient.
6. Detecting and monitoring any drug interactions.
7. Distinguishing between symptoms of drug toxicity and disease (may sometimes be the same, e.g. convulsions in an epileptic patient).
8. Guidance during the withdrawal of the drug therapy.

TDM can be divided into three phases: pre-analytical, analytical and the post-analytical phases.^[8] In Figure 1, the multidisciplinary approach to TDM is illustrated. It is important to emphasise the role of the different professionals in each phase.

Errors can occur during all three of these phases and these may compromise the TDM process. From the literature, it is evident that most errors occur in the pre- and post-analytical phases (see Figure 2).

The most common errors in the pre-analytical phase are, incomplete laboratory request forms,^[13] incorrect sample identification, inappropriate sample or sample volume or collection tube.^[14] An incomplete request form is one of the main reasons TDM cannot be implemented. In the analytical phase, standardisation, automation and technological advances have helped significantly to improve analytical reliability of laboratory results, but errors with equipment malfunction and sample mix-ups or interference still occur.^[11] In the post-analytical phase, most of the errors occur due to delayed result reporting, capturing of data and inappropriate assessment or interpretation of the results.^[11]

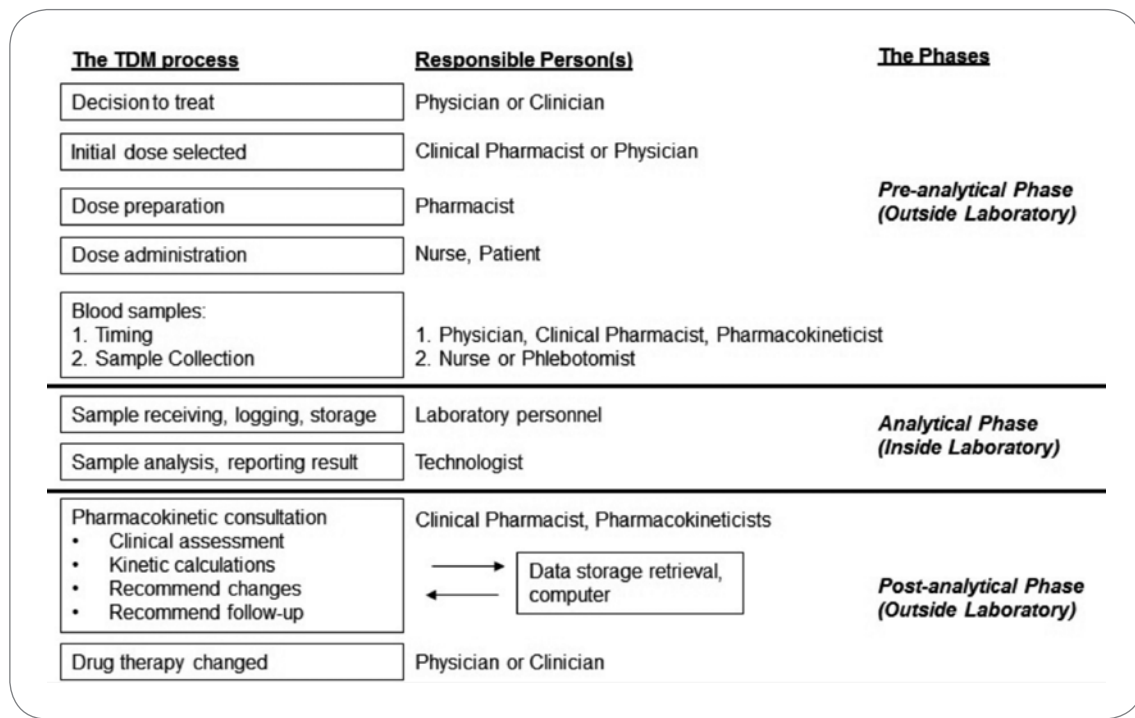


Figure 1: A multidisciplinary approach to individualising TDM (modified from literature^[8-9]).

This article aims to highlight the most commonly made human errors in the three phases of the TDM process and give some guidelines to minimise them. Each phase will be discussed individually.

ERRORS AND GUIDELINES FOR TDM IN THE PRE-ANALYTICAL PHASE

This phase is just as important for successful TDM as the other two phases and if mistakes are made during this phase, it is almost impossible to obtain reliable TDM outcomes.

Possible errors in the pre-analytical phase

The most common errors in the pre-analytical phase, comprising sample collection, gathering of patient information and transportation, are summarised in Table 1.

Important guidelines regarding the pre-analytical phase

1. Blood sample (serum/plasma)

The blood sample must be collected in an appropriate tube, which in the case of TDM is the plain red-topped collection tube, which provides a serum sample without a gel separator. Gel separator tubes should be avoided as the drug can be absorbed by the gel.^[4,15] According to a review article by Bowen and co-workers,^[16] several studies have shown that the separator gels absorb certain drugs such as the older antiepileptic drugs, for example carbamazepine and phenobarbital, tricyclic antidepressants, benzodiazepines and amiodarone.^[17-20] The guidelines therefore are when gel separator tubes are used the sample must be immediately centrifuged and the serum transferred to another tube for transportation and storage. The green-topped (heparin) or purple-topped (EDTA) blood collection tubes can also be used. Information on the blood collecting tube is very important to link it to the correct patient.

Sample collection from the patient must take place at the appropriate time in relation to the dosage interval.^[21] The patient's

TDM drug concentration is a direct result of their pharmacokinetic status at the time the sample was collected.^[3] The appropriate time for taking a blood sample for TDM is at steady-state concentration of the drug and the norm here will be a minimum of five half-lives at the current dosage regimen.^[5] Steady-state means the amount being given is equal to the amount being eliminated and equilibrium is reached.

2. Patient information^[5]

The following information is needed for a detailed TDM report:

1. Name and surname.
2. Age, weight, sex and ethnicity (the demographics of the patient).
3. The drug to be analysed for TDM.
4. The dosage of the drug or drugs, which includes dose, dosage form.
5. Time and date of last dose (to establish TDM result: Peak or trough level).
6. Time and date of sample taking.
7. The last TDM result for this drug if done by another laboratory.
8. Duration of treatment (to establish steady state).
9. The indication or reasons for the monitoring request.
10. Concomitant treatment with other drugs and their doses (drug interactions that may influence the pharmacokinetics of the drug in question).
11. Concomitant disease states, e.g. kidney problems.

3. Transportation and storage of the patient's sample

Transportation conditions of samples are very important. When a sample is transported, it should be kept cool and away from heat or sunlight. If a sample cannot be instantly delivered to the laboratory for analysis, it should be centrifuged immediately following collection, and the serum or plasma separated from the blood cell components and stored between -20°C and 4°C. It is

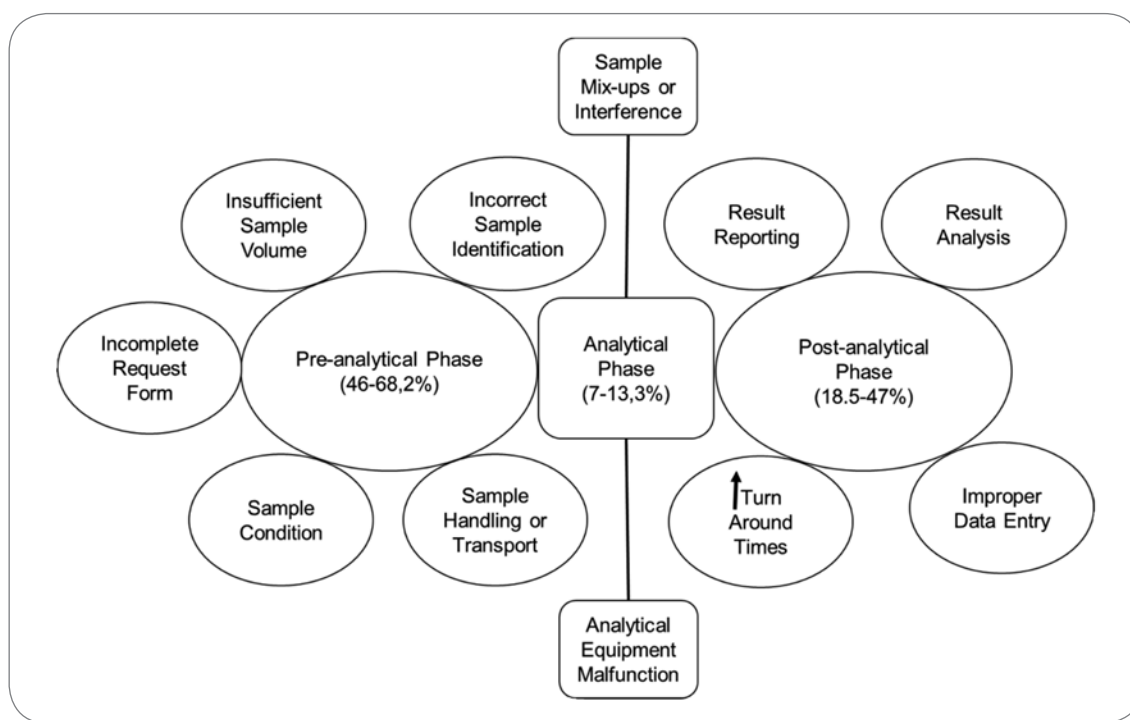


Figure 2: Types and rates of errors in the three phases in medical laboratory testing processes (modified from references^[10-14]).

Table 1

Sample collection	Patient information	Transportation
Wrong blood collection tube.	No information on the blood tube linking the patient to the sample.	Sample delayed during the transport to the laboratory, which can cause poor stability due to temperature changes.
Wrong time interval or time of sample not recorded.	Poor collection of the relevant patient information needed.	The sample was damaged or leaked out during transportation.
Not enough sample (serum or plasma), collected.	Wrong drug test was requested by the physician.	The patient's blood sample was sent to the wrong laboratory for analysis.
	Wrong drug test logged before sample was sent to the laboratory for analysis.	
	The patient has not taken his/her medicine as prescribed.	

vital the sample is kept cold until analysis is done, whereafter it should be stored again at -20°C. According to a review article of Peters, results from samples stored at room temperature, or in laboratory light, must be interpreted very carefully as partial degradation of the sample could occur.^[22]

ERRORS AND GUIDELINES FOR TDM IN THE ANALYTICAL PHASE

The analytical phase is where the laboratory and the analyst take responsibility for the sample analysis. In our experience, the laboratory and the analyst are often held responsible for errors made in the pre-analytical phase.

Possible errors in the analytical phase

Possible errors in the analytical phase are related to the samples, personnel and analysis. The patients' samples can be incorrectly labelled during preparation or analyses. Personnel performing the test who do not have the appropriate knowledge and training, or rush the analyses, may contribute to errors in this phase.

Analytical errors will also occur without regular and consistent maintenance and calibration of the analytical instruments. Other drugs taken concomitantly can interfere with the analysis and may cause incorrect interpretation of the results. Sample preparation steps are to be followed to the letter and errors can occur when the reagents are not stored under the correct conditions or replaced following their expiry dates. During TDM, clinical errors may also occur when a test result is reported in the wrong measurement unit.

Important guidelines regarding the analytical phase:

1. Samples

On arrival of the sample at the laboratory, a check must be performed to ensure the test was correctly logged into the laboratory data system before analysis can commence. In this regard, the following information must be noted before starting the sample preparation:

- The type of blood collection tube the sample was collected in.

- Is the serum or plasma volume sufficient for the test to be performed?
- Additional drugs the patient is taking, if reported, for possible analytical interference.

2. Personnel

The appropriate training of personnel is very important. A relevant degree or diploma in subjects such as clinical pharmacology, clinical biochemistry, clinical chemistry and analytical chemistry is vital. Special focus needs to be placed on the training of the specific analytical techniques and methods used in TDM (see point 3.2) and training on ISO guidelines for medical laboratories and GLP (Good laboratory practice) guidelines is crucial.^[23]

3. The analysis or test procedure

1. The analyst must ensure that he or she understands the test procedure and has the appropriate training on the analytical instrument and the technique or method used, as well as the relevant science it is based on.
2. Sample preparation is very important and the analyst must understand the technique and procedure to be followed, for example liquid-liquid extraction or solid-phase extraction.
3. Selecting the correct method of analysis is very important in TDM. Selectivity and sensitivity account for the main principles in the method selection process. There are a variety of analytical techniques to choose from: enzyme multiplied immunoassay technique (EMIT), radioimmunoassay (RIA), high performance liquid chromatography-ultraviolet (HPLC-UV), Gas chromatography-mass spectrometry (GC-MS) and liquid chromatography-mass spectrometry (LCMS/MS).^[3] Although EMIT and RIA techniques are more rapid, they are less sensitive and cross-reactivity and exogenous interferences can cause misinterpretation of patients' results.^[24] HPLC-UV, GC-MS and LC-MS/MS techniques can take longer to perform but are more sensitive and the results are more reliable. The EMIT and RIA techniques were cheaper in the past but lately HPLC techniques have become much more affordable per sample in comparison.
4. Only validated methods (preferably validated in the same laboratory) should be used and revalidation must be performed at least annually.
5. Daily performance of calibration samples and controls is warranted.
6. To be part of an external quality control, a sample-testing scheme is very important and forms part of a laboratory's external quality control programme.
7. Ensure the calibration samples and controls cover the complete therapeutic range of the drug to be tested.
8. The analyst must follow a methodology compliant with good laboratory practice (GLP) to link the patient's sample to the sample preparation, to the final sample to be placed in the analytical instrument and ultimately, the final result before it is reported.
9. Documentation of all the steps (from the sample preparation to the instrumental analysis to the report-

ing of the result) to be followed in the analysis or test procedure, with the guidance of a SOP (standard operating procedure) document, can prevent errors. Following the ISO guidelines can assist in creating a reliable system to prevent errors in the laboratory.^[23]

10. The analyst should know the limitations and possible interferences of the analytical method to be used.
11. Know all the possible effects of environmental conditions that can affect the analytical method.
12. When a result is questionable, the analyst must re-analyse it immediately if there is sufficient sample left or request more / an additional sample. If a questionable result is reported, an appropriate comment to the physician must accompany it.
13. Concomitant drugs (e.g. other anti-epileptics) that can be detected by the specific method must also be reported without extra cost, especially when those levels are outside the therapeutic ranges. In this situation, the patient's health comes first.
14. The analyst must also have adequate knowledge about the reagents and chemicals being used in the analytical method, with special reference to their stability and the number of samples that can be done before they are replaced according to their expiry date.

4. Reporting the test result

The appropriate unit in which to report the TDM results is also crucial for the correct interpretation of the results and depends on the concentration of the drug in the blood. Digoxin and Clozapine levels, for example, are measured in nano-grams per millilitre (ng/ml) and Carbamazepine and Efavirenz in micro-grams per millilitre (µg/ml).^[3] Some laboratories prefer to report their drug concentration results in molar units (mol/L), such as Digoxin (nmol/L), Carbamazepine and Theophylline (µmol/L) and Lithium (mmol/L).^[25-26]

Converting the results from mass per volume to moles per volume can be done in two ways. The first way is by following the basic chemistry formula:

$$n = \frac{m}{M}$$

Where: *n* = Drug concentration in moles per volume (mol/L)
m = Drug concentration in mass per volume (g/L)
M = Drug's molecular weight (g/mol)

For example with the drug Carbamazepine:

$$n = \frac{m \times 1000}{M}$$

$$n = \frac{4 \mu\text{g/ml} \times 1000}{236.26858}$$

$$n = 16.93 \mu\text{mol/L}$$

The second way is by multiplying the mass per volume result by a pre-calculated converting factor specific for each drug. The pre-calculated factors for each drug can be found in literature {Chapter 60: Reference information for the clinical laboratory: Table 60-2 Therapeutic and toxic levels of drugs^[3]}.

5. Storage after testing

Serum or plasma samples may be stored at 4°C in a refrigerator

from a week to a month, if the analysis needed to be repeated, although it may vary according to each drug's stability in serum or plasma. Samples can be stored for longer periods at -20°C and -80°C if needed, although in TDM, this does not make sense and one should rather obtain a new sample from the patient. In this case, the laboratory can set up its own protocol for repeating or re-analysing the sample or ordering a new sample.

ERRORS AND GUIDELINES FOR TDM IN THE POST-ANALYTICAL PHASE

Possible errors in the post-analytical phase

Errors in the post-analytical phase are usually a result of the errors made in the two previous phases. It is also important to remember to treat the patient and not a result. TDM is a holistic concept and without all the relevant information a blood concentration level is meaningless and a waste of money.

Important guidelines regarding the post-analytical phase.

1. Interpretation of the results

In this phase, where the final clinical interpretation must be made and a decision made as to whether the patient's dosage regimen must be altered, the physician, clinician or clinical pharmacokineticist needs the information discussed in the pre-analytical phase. At this stage, it is equally important to consider the patient's clinical condition and not interpret the results in isolation.^[21]

2. A patient's history database in TDM

Keeping an updated patient database of TDM results can contribute significantly to each patient's dosing regimen. A database can assist the clinician in making decisions that will be beneficial to the patient and their disease management.

COST EFFECTIVENESS OF TDM

The estimated cost of medical errors is very high^[27] and it is usually the patient who must pay these costs.^[28] In patients with certain disease conditions, e.g. epilepsy, TDM forms an integral part of their life because it involves continuous drug monitoring, sometimes monthly or even more than once a month. Therefore, the TDM process of individualisation of therapy should contribute to cost-effective patient management.^[29] Cost-effective TDM patient management has the ability to eventually decrease overall medical expenses for the patient and improve the quality of healthcare.^[30-32]

DISCUSSION

The most important errors that can occur in the pre-, analytical and post-analytical phases have been discussed. From the above, it is evident that each TDM laboratory must document and establish standard operating guidelines/procedures for all three phases to prevent problems and errors. If standard operating guidelines/procedures exist, it will be easy to rectify an error immediately and prevent any negative effects on the final result. Communication between all health professionals interacting with a TDM patient is very important to ensure the patient receives all the benefits. It is always important to consider the patient as an individual and not only as the measured concentration. The appropriate training of health professionals regarding the skills required during all the phases is of utmost importance. The laboratory can only take responsibility for analytical errors

and not errors made in the pre-analytical or post analytical phases. The physician, clinician or clinical pharmacokineticist cannot compensate for errors made in the pre-analytical and analytical phases. The patient's cooperation during the TDM process also contributes to the eventual benefits.

CONCLUSION

In conclusion, TDM is a multidisciplinary approach. If implemented correctly it can lead to an improvement in the patient's quality of life. Standard operating guidelines/procedures in the pre-analytical, analytical and post-analytical phases are of vital importance to prevent errors, which can lead to misinterpretation of drug levels.

TDM, THE FUTURE

Recently point-of-care (PoC) or on-site testing has become a focus point in healthcare. Several technological advances have been made in miniaturised PoC devices, for example in diabetes testing.^[33] It is hoped, for TDM, such devices will soon be a reality and PoC will give an immediate drug level result that will improve the patients' health and quality of life.

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