Therapeutic Drug Monitoring: Focus on Conditions in Indonesia

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ABSTRACT

It has been long recognized that large inter-individual variability is commonly observed in response to drug administration. The large response variability of certain drugs with narrow margin of safety may induce toxicity. To avoid this and to optimize the result of drug treatment, therapeutic drug monitoring (TDM) service has been routinely applied in hospitals in well-developed countries. For certain drugs, the TDM service has been shown beneficial and cost-effective.

In Indonesia, the TDM has not yet been implemented. There are three problems that hamper the implementation of TDM here, i.e. cost, the limited expertise to provide interpretation for result of drug assay, and the lack of communication with the clinicians. Today the patient safety issue is considered of paramount importance in the health care service in all hospitals. Therefore, it is now the time to commence the TDM service in Indonesia. This can be started with a pilot project in a large hospital, followed by the others. To avoid unnecessary wasting of funds, TDM should be limited for drugs which toxicity is not readily observed clinically.

Key words: therapeutic drug monitoring, response to drug, drug concentration, therapeutic range.

INTRODUCTION

It has been long recognized that great variation in response to drug administration in patient population causes a significant therapeutic problem. A drug at the same dose for the same indication may result in optimal therapeutic effect in some patients, but may fail to work or induce toxicity in the others. The problem is even more pronounced for certain drugs with narrow margin of safety such as aminoglycosides, digoxin, antidepressants, theophylline, phenobarbital, phenytoin, and immunosuppressants. Recently there is also a growing interest to apply TDM in patients treated with antineoplastic agents.1-3

In general, the variability of response to drug can be classified into two parts. The first one is in the pharmacokinetic domain which includes bioavailability of the drug, lipid solubility, patient compliance, pharmacokinetic drug interactions, volume of distribution of the drug, renal and liver function, dosing or medication errors, and polymorphism in drug metabolism. The second one is in the pharmacodynamic domain which includes pharmacodynamic drug interaction, the status of drug receptor, tolerance, and polymorphism in drug receptor.

To overcome the wide variability of drug response, an effective approach called Therapeutic Drug Monitoring (TDM) has been introduced in the 1970s. By definition, TDM refers to individualization of drug dosage by maintaining plasma or blood drug concentration of a patient within a targeted therapeutic range.4

The implementation of TDM has an impact on health care cost especially for drugs intended for long-term use. Certain drugs have to be administered for years or a life-time period such as antiepileptic and antiarrhythmic drugs. To avoid excessive and
unnecessary application, the indication of TDM should be limited for drugs with the following characteristics:\(^4,5\)
1) Narrow margin of safety; 2) Wide interindividual variation of effects; 3) The clinical effects of the drug are difficult to monitor; 4) The plasma concentration of the drug is well correlated with both the therapeutic and toxic effects; 5) Has a well defined therapeutic concentration range.

Today, the indications for carrying out TDM is not only limited to avoiding drug toxicity, but also to monitoring patient’s compliance, tailoring drug dose to the individual need of the patients, monitoring and detecting drug interactions.

**THERAPEUTIC DRUG MEASURING OR THERAPEUTIC DRUG MONITORING?**

Today, certain clinical laboratories in Indonesia provide the service of measuring drug concentration in plasma and they refer this as “therapeutic drug monitoring service” which is actually incorrect. If the service only provides the measurement of drug concentration in plasma, without interpretation, then the right term for this is “therapeutic drug measuring”. If the measurement includes interpretation of the measurement by a competent expert, then its called therapeutic drug monitoring.\(^6\) Interpretation of TDM should best be given by clinical pharmacologists or clinical pharmacists because of their education background. For an accurate interpretation, the following information is needed from the requesting clinicians:\(^3\)
1. Time of blood sampling in relation to the last dose (to estimate whether the sample was taken at the absorption or elimination phase)
2. Duration of the treatment with the current dose (to estimate whether or not the plasma level of the drug is already on its steady state)
3. Dosing regimen
4. Age and gender
5. Other drug therapy (possibly associated with drug-drug interaction)
6. Relevant disease state (liver and/or kidney disease)
7. The reason for asking TDM (suspect of drug toxicity, routine monitoring, compliance, lack of desired therapeutic effect)

Accurate interpretation of the assay result is of paramount important. Failure to do this may harm the patients. For example, a cardiologist sends a plasma sample of his patient for a TDM of digoxin after treating his patient for 2 days with digoxin. The dose given to the patient was 0.25 mg/day. He suspects that the patient is undertreated and should have been given a higher dose because of the poor therapeutic effect. The plasma concentration is 1 mcg/L. The therapeutic range of digoxin is 0.5-2.1 mcg/L. So he decides to double the digoxin dose. This decision may result in toxic effect to the patients because the digoxin plasma concentration in this patient is still increasing. The cardiologist should wait until 5 times the half-life of digoxin (i.e., 36 hours) before asking for a TDM for digoxin. So at least one week should elapse before the clinician can execute a TDM-based dose adjustment. In addition, sampling time should be best done at the time when the drug concentration declines to its lowest level, i.e. just before the next dose is administered (trough concentration). The appropriate time of blood sampling is so important, that without it TDM is rendered useless.\(^7\)

For drugs with extremely long half-lives of elimination (e.g., perhexilline, amiodarone), however, it is good to measure the blood concentration before the steady-state level is achieved because some individuals may develop toxicity due to impaired metabolism or renal excretion. In this case, the clinician should be aware that the drug concentration at this time point will still increase.

**COST-EFFECTIVENESS OF TDM**

To date there are only very few publications about the application of TDM. In terms of cost-effectiveness consideration, the most established indication for TDM is for aminoglycosides, followed by the less convincing indications for vancomycin, anti-epileptic drugs, and immunosuppressants.\(^8,9\) The term “less convincing” refers to the meaning that the application of TDM for these drugs is clinically useful but cost-effectiveness analysis has not been performed.

Currently, the cost for one measurement of plasma concentration in one private lab in Jakarta ranges between Rp 390.000,- (for tacrolimus) to Rp 635.000,- (for cyclosporine) (equal to US $43.- to US $70.-), which has not yet included the cost of interpretation of the result. Obviously, this would be too burdensome for most of the patients in Indonesia. Like many other clinical chemistry tests, the cost per test can be considerably reduced if the volume of demand is sufficiently large. Too small number of orders leads to wasting of unused test kits at the time of expiry, thus causing high cost of the test. Most likely the extremely high cost of TDM in Indonesia today is associated with this issue. One publication from India in 1999 reported that the cost there was only £3-4 per drug test.\(^10\)

The majority of hospitalized patients in Indonesia
are those from the low-income. In the hospital, they are accommodated in the 3rd class with the room rate ranging from Rp.30,000 – Rp.100,000,- (equal to US $3.3 – US $11.1) per day. Obviously the cost of TDM is unaffordable for majority of Indonesian patients. At the present time, the cost for TDM is not yet covered by the Health Insurance system in Indonesia. Certainly, this needs to be revised in the future.

**ASSAY METHODS**

Equipments required for TDM constitute a major problem because of their price. Equipments commonly used in the TDM include high performance liquid chromatography (HPLC), radioimmunoassay (RIA), fluorescence polarization immunoassay (FPIA), enzyme mediated immunoassay (EMIT), enzyme linked immunosorbent assay (ELISA). The HPLC method is relatively inexpensive and it can also measure simultaneously more than one drugs in plasma. For TDM, the unbound drug concentration is usually assayed because the protein-bound fraction is inactive pharmacodynamically. The measurement of the unbound fraction of a drug in plasma will require an ultrafiltration process. This method is particularly useful for epileptic patients who are taking more than one anticonvulsants. Its shortcoming, however, is time consuming and requires highly trained staff. Therefore, it is not commonly used today. Validation of the analytical method is of paramount important. The ultrafiltration and the extraction procedures also render this method less practical. The HPLC analytical methods, however, are still useful for analyzing drugs which cannot be assayed with immunoassay methods (e.g. amiodarone, perhexiline).

RIA is an analytical method which is uncommonly used due to the problems caused by the radioactive waste products. Today the most commonly used analytical methods for TDM are FPIA, EMIT, and ELISA. The immunoassay tests are more expensive but provide more immediate results, which are very much needed by the clinicians to adjust a drug dose without having to wait for too long a time. The ideal timeframe for a laboratory turn around time should not exceed the dosing interval, and this can be well managed if an immunoassay method is used. Cost constraint, however, is the major reason why in many laboratories the assays are performed in batches which results in the extension of the turnaround time.

The immunoassay is assumed to be specific. In certain cases, however, it also measures the metabolites of the parent drug or other drug-like substances, thus resulting in an elevated reading of the drug concentration. The biological specimen required for TDM is plasma or serum. The anticoagulant commonly used is heparin. The plasma or serum samples should be immediately assayed because the result is urgently needed by the clinicians for dose adjustment. In case this cannot be done, the plasma or serum sample should be frozen immediately. For the TDM of cyclosporin, whole blood is used.

**WHAT ARE THE PROBLEMS IN INDONESIA?**

The application of TDM in Indonesia (and perhaps also in other developing countries) may be confronted with some significant problems. The first one is the operational cost of the TDM services. At the present time, as far as we know, there is no hospital in Indonesia providing the TDM service. The cause is not obvious, but it could be due to the high cost and the ignorance of many clinicians. If the demand is low, the cost will be automatically high because of the short shelf-life of the assay kits. Meanwhile the high cost of the TDM services will, in turn, reduce the demand, thus causing a vicious circle. To overcome the problem, the author would suggest to start a pilot project in a large hospital with potentially high demand of the service (e.g., the Cipto Mangunkusumo Hospital in Jakarta). Other hospitals in vicinity can share the use of the facility without having to spend too much for purchasing the the equipment and the assay kits. Once the pilot project turns successful, other large hospitals may follow.

Interpretation, as described above, is an important issue in TDM. The blood sampling should be done in appropriate time by considering the moments when the drug attains its peak, trough, and steady-state levels in plasma. Failure to do this may result in harmful effects to the patient. The clinicians who apply the TDM should consult to the clinical pharmacologists or clinical pharmacists who are well trained for this job. Despite the very small number of clinical pharmacologists and clinical pharmacists we have currently in Indonesia, they appear to be sufficient if we start now with a pilot project. A good communication and cooperation between the clinical departments, clinical chemistry laboratories, and clinical pharmacology departments is of paramount important. In addition, it appears that one of the reasons why TDM has not yet been implemented now in this country is likely caused by the less effective communication between the clinicians, the clinical pathologists, and clinical pharmacologists.

It should be realized that despite its usefulness,
TDM remains as a tool to assist the clinicians in making their therapeutic decision. The result of assay does not necessarily dictate the clinician to adjust dose in all conditions. For example, an epileptic patient is being treated with phenytoin. He is doing well and has neither seizure or signs of toxicity for months. In a TDM, however, his phenytoin plasma concentration was only 70% of the normal targetted therapeutic plasma level. In this case, despite being in a sub-therapeutic plasma concentration, no dose escalation is needed for this patient. This is an example where an appropriate interpretation is needed in TDM.

Another important issue is that an appropriate TDM service always requires sufficient information from the clinician. This includes the dosing regimen, duration of treatment with the current dose, the time of the last dosing, the concomittant medications, relevant disease state, the reason for request (e.g., monitoring for compliance, lack of therapeutic effect, or suspicion of toxicity). Unfortunately, many physicians still ignore this without realizing that the information is very important for constructing a good interpretation. It is therefore very important to provide sufficient information for the clinicians prior to launching the TDM.

Despite more and more new kits are commercially available in the market, the clinicians should not request TDM for drugs whose toxicity can be easily measured, e.g. warfarin (the INR should be used for this) and betablockers. The TDM requests should also be restricted to drugs with narrow margin of safety. Failure to do this will result in insignificant clinical benefit and a large wasting of fund.

CONCLUSION

Therapeutic drug monitoring is an important tool to assist clinicians in adjusting dose of drugs with narrow margins of safety and difficult-to-measure clinical toxicity. Until now there is no hospital in Indonesia providing the TDM service. Cost appears to be a major obstacle to apply TDM in Indonesia, and perhaps in many other developing countries. The other major issue in TDM is the interpretation of drug concentration in plasma or serum. If a laboratory only measures the drug concentration without interpretation, the suggested term for this service is “therapeutic drug measurement” rather than “therapeutic drug monitoring”. Without appropriate interpretation, the clinicians who request the TDM may gain little benefit. In their education program, clinical pharmacologists and clinical pharmacists receive special training for providing this interpretation.

The timing of blood collection is also another issue that deserves attention. It depends on the specific purpose of the TDM. Incorrect sampling time, coupled with inaccurate interpretation, may expose the patient to harmful effect.

Considering the relatively high cost of TDM and the scarcity of clinicians’ request today, it is suggested the TDM in Indonesia be started with a pilot project in a large hospital. If it is successful, the TDM project may be extended gradually to other hospitals throughout the country.

REFERENCES