Therapeutic drug monitoring: which drugs, why, when and how to do it

RA Ghiculescu, Senior Clinical Pharmacology Registrar, Department of Clinical Pharmacology, Princess Alexandra Hospital, Brisbane

Summary

Therapeutic drug monitoring of concentrations of drugs in body fluids, usually plasma, can be used during treatment and for diagnostic purposes. The selection of drugs for therapeutic drug monitoring is important as the concentrations of many drugs are not clearly related to their effects. For selected drugs therapeutic drug monitoring aims to enhance drug efficacy, reduce toxicity or assist with diagnosis. Despite its apparent advantages, it has inherent limitations. Some large hospitals have services which provide support with drug monitoring and interpretation of results.

Key words: pharmacokinetics.

(Aust Prescr 2008;31:42–4)

Introduction

The monitoring of therapeutic drugs involves measuring drug concentrations in plasma, serum or blood. This information is used to individualise dosage so that drug concentrations can be maintained within a target range.[1]

Drug concentration at the site of action cannot be routinely measured, but the desired or adverse effects may correlate better with plasma or blood concentrations than they do with dose. For a few drugs, concentration measurements are a valuable surrogate of drug exposure, particularly if there is no simple or sensitive measure of effect.

When there is a large inter-individual variation between dose and effect, for example when there is large pharmacokinetic variation, individualising drug dosage is difficult.[1] This is particularly relevant for drugs with a narrow target range or concentration-dependent pharmacokinetics. Similarly, variations within an individual can occur over time for a range of reasons with some drugs, and therapeutic drug monitoring could then be useful.

Therapeutic drug monitoring involves not only measuring drug concentrations, but also the clinical interpretation of the result. This requires knowledge of the pharmacokinetics, sampling time, drug history and the patient's clinical condition.

Which drugs?

When an effect, such as changes in blood pressure, pain or serum cholesterol is readily measured, the dose of a drug should be adjusted according to the response. Monitoring drug concentration is more useful when drugs are used to prevent an adverse outcome, for example, graft rejection or to avoid toxicity, as with aminoglycosides. A drug should satisfy certain criteria to be suitable for therapeutic drug monitoring. Examples include:

- narrow target range
- significant pharmacokinetic variability
- a reasonable relationship between plasma concentrations and clinical effects
- established target concentration range
- availability of cost-effective drug assay.

The most commonly monitored drugs are probably carbamazepine, valproate and digoxin. However, there is little evidence that monitoring concentrations of anticonvulsants improves clinical outcomes when the drugs are used to treat mood disorders.

Table 1 shows some of the drugs that meet these criteria.

Indications ('why do it')

Drug assays are costly, so the reason for monitoring and the additional information to be gained (if any) should be carefully considered. For some drugs, therapeutic drug monitoring helps to increase efficacy (vancomycin), to decrease toxicity (paracetamol) and to assist diagnosis (salicylates). Routine monitoring is not advocated for most drugs. Only clinically meaningful tests should be performed.[1]

The appropriate indications for therapeutic drug monitoring (and examples) include:

- toxicity
  - diagnosing toxicity when the clinical syndrome is undifferentiated (unexplained nausea in a patient taking digoxin)
  - avoiding toxicity (aminoglycosides, cyclosporin)

- dosing
  - after dose adjustment (usually after reaching a steady state)
  - assessment of adequate loading dose (after starting phenytoin treatment)
  - dose forecasting to help predict a patient's dose requirements[1] (aminoglycosides)
- monitoring
  - assessing compliance (anticonvulsant concentrations in patients having frequent seizures)
  - diagnosing undertreatment (particularly important for prophylactic drugs such as anticonvulsants, immunosuppressants)
  - diagnosing failed therapy (therapeutic drug monitoring can help distinguish between ineffective drug treatment, non-compliance and adverse effects that mimic the underlying disease).

The target concentration may depend on the indication. For example, the recommended concentration for digoxin depends on whether it is being used to treat atrial fibrillation or congestive heart failure.[2]

Table 1

Drugs suitable for therapeutic drug monitoring

Drug	Target range *
Drugs regularly monitored in clinical practice	
digoxin	0.8–2 microgram/L and < 0.01 microgram/L in refractory heart failure
lithium – acute mania	0.8–1.2 mmol/L
– maintenance	0.4–1.0 mmol/L
perhexiline	0.15–0.6 mg/L
phenytoin	10–20 mg/L
cyclosporin	50–125 microgram/L (serum or plasma) 150–400 microgram/L (whole blood) Concentrations differ for various clinical settings
sirolimus	5–15 microgram/L (whole blood)
tacrolimus	5–20 microgram/L (whole blood)
Drugs for which monitoring may be useful	
amiodarone	1–2.5 mg/L
carbamazepine	5–12 mg/L
flecainide	0.2–0.9 mg/L
lamotrigine	1.5–3 mg/L
salicylate	150–300 mg/L
sodium valproate	50–100 mg/L
vancomycin	Trough 10–20 mg/L

* Concentrations may vary between laboratories

Timing of the plasma sample ('when to do it')

Unless therapeutic drug monitoring is being used to forecast a dose or there are concerns about toxicity, samples should be taken at steady state (4–5 half-lives after starting therapy).[1,3]

At steady state, plasma concentration is usually proportional to receptor concentration. Some drugs, such as perhexiline, which has a very long half-life in patients who are 'poor metabolisers', should be monitored before steady state is achieved to prevent toxicity developing after the first few doses. Another example where early monitoring may be useful is after phenytoin loading, where measurement of the plasma concentration can give a preliminary indication of adequate dosing.

The timing of the collection of the sample is important as the drug concentration changes during the dosing interval. The least variable point in the dosing interval is just before the next dose is due. This pre-dose or trough concentration is what is usually measured. For drugs with long half-lives such as phenobarbitone and amiodarone, samples can be collected at any point in the dosage interval.[1,3]

Correct sample timing should also take into account absorption and distribution. For example, digoxin monitoring should not be performed within six hours of a dose, because it will still be undergoing distribution and so plasma concentrations will be erroneously high.[1,3]

Occasionally, sampling at the time of specific symptoms may detect toxicity related to peak concentrations of, for example, carbamazepine and lithium.

For once-daily dosing of aminoglycosides, the timing of the blood sample is determined by the method of monitoring. For example, it is collected 6–14 hours post-dose when a nomogram is used, or twice within the dosing interval to calculate the area under the concentration-time curve.[4,5] When aminoglycosides are prescribed in multiple daily doses to treat, for example, enterococcal endocarditis, then trough samples are measured to minimise toxicity and assess whether concentrations are adequate for efficacy.

Therapeutic drug monitoring request ('what to document')

Drug assays may be requested for therapeutic drug monitoring or for clinical toxicology purposes.[5] For therapeutic drug monitoring the information required to allow interpretation of the result should include the time of the sample collection, the time of the last dose, the dosage regimen and the indication for drug monitoring.[1,3]

Interpretation

Drug concentrations need to be interpreted in the context of the individual patient without rigid adherence to a target range. For example, if a patient has an anticonvulsant drug concentration just below the target range, but is not having seizures, an

increase in dose is probably not required. For a few drugs, monitoring drug concentration is a helpful adjunctive measure. Before making dose adjustments, it is important to consider if the sample was taken at the correct time with respect to the last dose, if a steady state has been reached and whether the patient has adhered to their treatment. There are other considerations, for example, the serum potassium should be noted when interpreting digoxin concentrations as toxicity can occur at a therapeutic concentration if there is hypokalaemia.

Most drug assays measure total drug concentration (bound and unbound drug), but only the unbound drug interacts with its receptor to produce a response. The unbound fraction may be affected by factors such as serum albumin concentration, displacement by an interacting drug and renal failure. This is important for drugs like phenytoin. If phenytoin's unbound fraction doubles from 10% to 20%, the target range based on total phenytoin concentration should be halved. If dose adjustments are made according to the usual target range, toxicity may result.

Measuring and monitoring

Drug concentrations should be measured within a clinically useful timeframe in laboratories with appropriately trained staff and subject to quality assays.[3] The ideal laboratory turnaround time should be shorter than the dosing interval, however, due to cost, assays are performed in batches which may lengthen the turnaround time.

Plasma drug concentrations are reported either in mass or molar units. Reporting in mass units with attached conversion formulas may assist with interpretation of results.[3]

Differences exist between laboratories and validated target ranges should accompany results to assist clinicians with safe and effective prescribing.[3]

Some institutions provide drug monitoring and interpretive services which may help to improve the safety, efficacy and cost-effectiveness of clinical services. These therapeutic drug monitoring services also have an educational role by promoting the principles of rational prescribing and quality use of medicines.[3]

Limitations

Apart from the limited number of drugs amenable to therapeutic drug monitoring, there are also inherent limitations, including the scientific accuracy of the drug assays, laboratory variability in reporting, limited accessibility in rural Australia and the validity of suggested target ranges.[1,3]

The target range describes a range of drug concentrations associated with a reasonable probability of efficacy without undue toxicity in the majority of patients. It is not well described for most drugs and is often based on a very limited number of data points.[1,2]

Active metabolites (for example carbamazepine-10,11-epoxide) may contribute to the therapeutic response but are not routinely measured.

Conclusion

The drug concentration is complementary to and not a substitute for clinical judgement so it is important to treat the individual patient and not the laboratory value. Drug concentrations may be used as surrogates for drug effects so therapeutic drug monitoring may assist with dose individualisation. It can also be used to detect toxicity, so therapeutic drug monitoring can optimise patient management and improve clinical outcomes. Careful selection of drugs to be monitored should occur. Regular monitoring of many drugs is not required in a clinically stable patient.

Professor Peter Pillans is acknowledged for his assistance in the preparation of this article.

References

1. Birkett DJ. Therapeutic drug monitoring. Aust Prescr 1997;20:9-11.
2. Chatterjee K. Congestive heart failure: what should be the initial therapy and why? Am J Cardiovasc Drugs 2002;2:1-6.
3. Gross AS. Best practice in therapeutic drug monitoring. Br J Clin Pharmacol 1998;46:95-9.
4. Begg EJ, Barclay ML, Duffull SB. A suggested approach to once-daily aminoglycoside dosing. Br J Clin Pharmacol 1995;39:605-9.
5. eTG complete. Therapeutic Guidelines Ltd. 2007 Nov.

Conflict of interest: none declared

National Medicines Symposium 2008

Wednesday 14 – Friday 16 May 2008, National Convention Centre, Canberra

The theme for the fifth biennial symposium is 'QUM: what does it really mean for you? The science, the policy and the practice'. Co-hosted by the National Prescribing Service and Pharmaceutical Health And Rational use of Medicines (PHARM) Committee, the symposium will cover a variety of perspectives and views from health professionals, the pharmaceutical industry, academics, policy makers and regulators, consumers and community organisations. NMS 2008 will be a platform for sharing expertise and experience, and exploring international and national best practice in QUM.

For registration and more information, see www.nps.org.au