‘Just a repeat’

When drug monitoring is indicated

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Background

Therapeutic drug monitoring, the measurement of plasma or blood concentrations of a medication to assist the management of patients, is commonly performed by general practitioners and specialists alike. However, established therapeutic ranges are only available for a limited number of medications.

Objective

This article outlines the basics of therapeutic drug monitoring, including the drugs for which monitoring is suitable and when, how and why it should be performed in general practice.

Discussion

Therapeutic drug monitoring is generally only indicated when medications have specific characteristics (eg. a narrow therapeutic index), where there is an established therapeutic range, where the consequences of undertreatment cannot be recognised clinically and can be serious (eg. seizure) and/or if toxicity is suspected. Commonly used medications where therapeutic drug monitoring is indicated include some anti-epileptic drugs (eg. phenytoin, carbamazepine), lithium and digoxin. For the majority of medications, therapeutic drug monitoring is unlikely to assist management and should not be performed.

Keywords

drug monitoring; anticonvulsants; lithium; digoxin

CPD

Therapeutic drug monitoring (TDM) is the measurement of plasma/blood concentrations of a particular drug. This information is subsequently interpreted to individualise and optimise a patient’s dosage regimen and therapeutic outcomes[1] by maintaining drug concentrations within a target therapeutic window.[2]

Therapeutic drug monitoring is utilised in a variety of clinical contexts (such as antimicrobial monitoring or in the setting of drug overdose) for a wide range of drugs in the hospital environment. However, this article will focus on drugs commonly encountered by general practitioners in the community setting, for which monitoring is warranted.

Indications for pharmacokinetic monitoring

Indications for employing TDM may include:

- after initiating treatment
- after adjusting dose
- if treatment is failing
- if non-compliance is suspected
- when starting or stopping a potentially interacting drug
- if there is a change in a patient’s physiology (eg. pregnancy, renal or hepatic impairment)
- to assess for drug toxicity or suspected overdose
- to confirm abstinence
- to assist diagnosis – adverse drug effects may mimic disease state.[3]

For the majority of drugs, routine monitoring is not supported[4] and should only occur if it can be accurately interpreted and subsequently contribute to patient management.

Resources should not be expended on monitoring drug concentrations if they are unable to be interpreted and subsequently do not contribute to patient management.[5] However, large inter-individual variation in the dose-response relationship can make drug dosage difficult.[5] Sources of pharmacokinetic variability in a patient’s response to drugs include age, gender, organ function, drug interactions and drug metabolising capacity.[2] Therapeutic drug monitoring may assist GPs to overcome this variability.[6]

Drugs for which monitoring may be helpful

Criteria that a drug should satisfy to be suitable for TDM include:

- marked pharmacokinetic variability (inter- or intra-individual)[1]
- a narrow therapeutic index
- an evidence based therapeutic range

- a defined concentration-effect relationship
- serious consequences (eg. seizures, transplant rejection) if there is therapeutic failure
- no appropriate direct measure of desired therapeutic effect[5]
- a suitable and accessible laboratory assay.[6]

When and how to monitor

Correct drug sampling time is important. Pre-dose trough concentrations are used most commonly, as they represent the least variable point in the dosing interval and therapeutic ranges have often been established using trough concentrations. However, once steady state is reached, any point in the dose interval may be used for drugs with long half-lives (eg. digoxin or phenytoin).[2] Expedient concentration monitoring (before achieving steady state) is warranted if toxicity is suspected or there is poor therapeutic control.[5] Sampling when symptoms are present may detect peak concentration toxicity,[7] but should be interpreted with caution considering that the therapeutic range is likely to have been established using a trough concentration.

Interpretation of drug concentration

Information required to facilitate correct interpretation of a drug concentration includes:

- time of blood collection
- dosage regimen (including dose, dose form, time of drug administration and duration of therapy)
- patient characteristics (eg. age, gender, concomitant disease, ethnicity)
- concomitant medications
- indication for monitoring
- therapeutic range and pharmacokinetics of the drug.[5]

Because therapeutic ranges are predominantly derived from small studies, there will be individuals for whom lower concentrations are adequate and those who experience adverse events, even within the published therapeutic range. Hence it is important to interpret drug concentrations in the patient's clinical context.[2]

Table 1 outlines established therapeutic ranges for commonly used drugs that require monitoring or that may be encountered in the general practice setting. Ranges from different laboratories may vary.

Interpretive services can be accessed via the measuring pathology laboratory or via a clinical pharmacologist (often based at a large tertiary centre).

Table 1 summarises interactions that may significantly influence serum drug concentrations. Potential mechanisms of pharmacokinetic interactions include:

- via induction or inhibition of cytochrome P450 (CYP450) isoenzymes (eg. CYP3A4 with carbamazepine[6,8] and both phenytoin and valproate with CYP2C isoenzymes)[8]
- via glucuronidation (as is the case with lamotrigine and sodium valproate)[8]
- via inhibition or induction of P-glycoprotein (digoxin is a P-glycoprotein substrate)[6]
- via protein binding (this affects sodium valproate[8] and phenytoin[1])
- via alteration of renal excretion (as may occur with lithium[6]).

Monitoring anti-epileptic drugs

Therapeutic failure of anti-epileptic drugs is associated with potentially dangerous consequences. Plasma concentrations of many anti-epileptic drugs poorly correlate with efficacy or toxicity,[9] but TDM can be used to optimise treatment of some anti-epileptic drugs. There is reasonable evidence for monitoring phenytoin, carbamazepine and sodium valproate. Although most specialists would advocate TDM for lamotrigine, its therapeutic range has not yet been definitively established.[1] In the absence of well established therapeutic ranges, TDM is not recommended for gabapentin, topiramate, tiagabine,[1,10] levetiracetam[1] or vigabatrin.[10]

There is little evidence regarding the application of therapeutic ranges for epilepsy when anti-epileptic drugs are used for other indications (eg. migraine prophylaxis, mood disorders).[1,10] However, carbamazepine's anti-epileptic therapeutic range (*Table 1*) can be used to help avoid toxicity.[9]

Measurement of steady state plasma concentrations may be useful to determine the drug concentration associated with seizure control, without significant side effects, as a reference for future therapeutic decisions.[11] The plasma concentration should be rechecked after a significant dose change, once the new steady state is reached.[9]

Although the majority of anti-epileptics display first order kinetics (where a change in dose should result in a proportional change in plasma concentrations),[1] individualised dosing is warranted in some cases due to inter-individual variability in pharmacokinetics.[11] Sodium valproate and phenytoin display nonlinear kinetics,[2] making monitoring and adjusting doses complex. A disproportionately large change in plasma concentration may result from only a moderate dose increase.[1]

The therapeutic concentration range for total phenytoin is 10–20 mg/L. If total plasma phenytoin concentration is ≤5 mg/L, phenytoin dose can be increased by up to 100 mg/day. If the concentration exceeds 5 mg/L, phenytoin dose may be increased by no more than 30 mg/day.[6]

Phenytoin is highly bound to albumin,[1] but it is unbound/free phenytoin that is pharmacologically active.[2] Assays using plasma or blood measure total phenytoin,[2] but patients with low albumin have a greater free fraction of phenytoin[1] and total drug concentrations must be interpreted differently to avoid potential toxicity.[2]

The 'effective' plasma concentration can be estimated by using the modified Sheiner-Tozer equation (which accommodates for an increase in the unbound phenytoin fraction):[6]

phenytoin plasma concentration (adjusted) = phenytoin plasma concentration (reported)/[(0.02 x serum albumin in g/L) + 0.1]).

Monitoring lithium

As lithium has a narrow therapeutic index, its serum concentration should be carefully monitored. Patients should be warned to report symptoms that might indicate their lithium dose requires reduction, such as unsteadiness, confusion, nausea, diarrhoea or worsening tremor.[9]

Table 1. Therapeutic monitoring of commonly used drugs

Drug	Therapeutic range	Half life (hours)	Sampling time	Time to steady state (days)
Carbamazepine	Generally 4–12 mg/L (upper limit subject to debate)[6,7]	10–17[1]	Pre-dose trough[1]	7–10[1]
Digoxin	0.5–2.0 µg/L[6] (0.5–0.8 µg/L in patients with heart failure)[6]	36[6]	Trough or >8 hours post-dose[7]	7–10[1]
Lamotrigine	3–14 mg/L[7] (not well established)[1]	~ 25 (varies greatly, 14–59)[1]	Pre-dose trough[1]	5 (longer with concomitant valproate)[10]
Lithium	0.6–1.2 mmol/L[2] (clinical toxicity can occur at lower concentrations)	8–55 (mean 18–24)[18]	Pre-dose trough[1] (>12 hours after last dose)	3–7[1]
Phenytoin	10–20 mg/L[1,2,7]	~24[1]	Trough (any time once at steady state)[1]	5–7[1]
Sodium valproate	50–100 mg/L[1,2,7]	15[1]	Pre-dose trough[1]	3–5[6]

Note: Local laboratory reference ranges should be consulted

Adverse effects	Significant pharmacokinetic drug interactions	
	May increase concentration	**May decrease concentration**
Ataxia, dizziness, diplopia, vertigo, aplastic anaemia, leucopenia, gastrointestinal irritation, hepatotoxicity, hyponatraemia, skin rash, Stevens-Johnson syndrome[1]	**CYP450 enzyme inhibitors:** • azole antifungals[6] • dextropropoxyphene[1] • diltiazem[6,8] • fluoxetine[6] • fluvoxamine[6] • grapefruit juice[8] • HIV protease inhibitors[6] • isoniazid[1] • macrolide antibiotics[1] • quetiapine[6] • verapamil[8]	**CYP450 enzyme inducers:** • phenytoin[1] • rifampicin[1]
Electrolyte imbalance, central nervous system disturbances, visual disturbances, arrhythmia, conduction disturbances, gastrointestinal upset, rash[17]	**P-glycoprotein inhibitors:** • amiodarone[6] • azole antifungals[6] • carvedilol[6] • cyclosporin[6] • macrolide antibiotics[6] • ritonavir[6] • verapamil[6] **Other:** • alprazolam[8] • diltiazem[6] • nifedipine[6] • spironolactone[6]	**P-glycoprotein inducers:** • rifampicin[6] • hypericum perforatum[6] (St John's wort) **Other:** • cholestyramine[6] • neomycin[6] • sulfasalazine[6]
Dizziness, diplopia, ataxia, incoordination, confusion, gum hyperplasia, lymphadenopathy, hirsutism, osteomalacia, facial coarsening, skin rash, Stevens-Johnson syndrome[1]	**Sodium valproate** (Note: increased risk of Stevens-Johnson syndrome)[1]	**Induce glucuronidation:** • carbamazepine[6] • combined oral contraceptive pill[6] • HIV protease inhibitors[6] • phenytoin[8] • rifampicin[6]
Nausea, diarrhoea, vertigo, muscle weakness, tremor, fatigue, thirst, polyuria, leucocytosis, weight gain, oedema, hypothyroidism[17]	**Impair renal excretion:** • ACEIs[6] • ARBs[6] • diuretics (loop and thiazide)[6] • NSAIDs (including selective cyclooxygenase-2 inhibitors)[6]	**Increase renal excretion:** • sodium bicarbonate[6]
Dizziness, diplopia, ataxia, incoordination, confusion, gum hyperplasia, lymphadenopathy, hirsutism, osteomalacia, facial coarsening, skin rash, Stevens-Johnson syndrome[1]	**CYP450 enzyme inhibitors:** • amiodarone[1] • azole antifungals[6,8] • carbamazepine[6] • diazepam[6] • diltiazem[6] • fluoxetine[1] • fluvoxamine[6] • isoniazid[1] • sodium valproate (chronic)[6] • sulphonamides[1] • topiramate[8] • trimethoprim[8]	**CYP450 enzyme inducers:** • carbamazepine[1,6] • ciprofloxacin[6] • diazepam[6] • HIV protease inhibitors[6] • hypericum perforatum[6] • rifampicin[1] **Protein binding:** • sodium valproate (acute)[6] **Other:** • parenteral feeding[1,8] • folic acid[6] • vigabatrin[6]
Ataxia, sedation, tremor, hepatotoxicity, thrombocytopenia, gastrointestinal irritation, weight gain, transient alopecia, hyperammonaemia[1]		**CYP450 enzyme inducers:** • phenytoin[1] • carbamazepine[1] • rifampicin[1]

At therapeutic concentrations, lithium can produce a fine tremor, muscular weakness, extrapyramidal symptoms or electroencephalogram changes (eg. increased amplitude and generalised slowing).[9]

Lithium toxicity usually occurs at concentrations greater than 2 mmol/L, but may develop at considerably lower concentrations, especially in older people.[9]

Lithium is excreted renally and accordingly, patients with renal impairment require dose reduction and more intensive monitoring. Caution must also be exercised in patients with congestive heart failure.[9] Lithium toxicity may be potentiated by intercurrent illness, hypovolaemia or use of medications that may reduce the renal clearance of lithium (eg. diuretics, non-steroidal anti-inflammatory drugs [NSAIDs], angiotensin-2 receptor blockers [ARBs] and angiotensin converting enzyme inhibitors [ACEIs]).[9]

Serum lithium concentration should be measured at least every 3–6 months after achieving a stable therapeutic concentration.[9]

Monitoring digoxin

Digoxin has a narrow therapeutic range[6] and although toxicity may occur within the therapeutic range,[12] very few adverse effects occur at plasma concentrations <0.8 µg/L.[6]

The risk of digoxin toxicity is potentiated in elderly patients and in those with renal impairment (as digoxin is predominantly renally cleared), electrolyte disturbances (eg. hypokalaemia, hypomagnesaemia, hypercalcaemia), acidosis, hypoxia, hypothyroidism or co-administered P-glycoprotein inhibitors.[6] Dose reduction and close monitoring of digoxin concentration and clinical response is warranted.

Loading doses of digoxin should be halved in the elderly and in those with renal impairment (creatinine clearance <60 mL/min). Maintenance doses of digoxin should be halved in the elderly and may be as low as 62.5 µg on alternate days in patients with severe renal impairment[6] (*Table 1*).

Lower target concentrations should be considered in patients with heart failure, for whom increased morbidity and mortality may be associated with higher concentrations.[6]

The reproducibility of the digoxin assay is such that through the course of digoxin therapy, patient samples analysed by different laboratories and medical practitioners may be unacceptably inconsistent.[13]

Digoxin concentrations analysed using a range of immunoassays may simultaneously report subtherapeutic, therapeutic or toxic concentrations.[13] Such variation may arise because of substances in a patient's blood that interact with the antibody used in various commercial digoxin immunoassays.[13] These substances include digoxin-like immunoreactive substances, which are large molecular weight compounds that are increased in a range of clinical conditions such as congestive cardiac failure,[14] as well as spironolactone, its metabolite canrenone and other steroids[15] and herbal medicines (eg. ginseng).[16]

This extensive variation in digoxin monitoring has significant implications, as it makes drug concentrations difficult to interpret.[13] Clinical monitoring of heart rate and adverse effects may be more helpful than TDM.

Key points

- Although routine TDM is not supported for the majority of drugs, in selected cases it may assist GPs to individualise and optimise a patient's dosage regimen and therapeutic outcomes.
- Indications for employing TDM should be carefully considered and drugs should satisfy certain criteria to be suitable for TDM.
- Drugs encountered in general practice that may warrant TDM include some anti-epileptics and digoxin.
- Regular TDM is indicated for lithium.
- For some drugs, clinical monitoring may be more helpful than TDM and in all cases, it is imperative that drug concentrations are interpreted in the patient's clinical context.

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References

1. Patullo C, Donovan P, Kubler P, editors. RBWH prescribing guidelines. Brisbane: Queensland Health, 2012.
2. Birkett DJ. Therapeutic drug monitoring. Australian Prescriber 1997;20:9–11.
3. Begg EJ. Instant clinical pharmacology. 2nd edn. Victoria: Blackwell Publishing, 2008.
4. Ghiculescu RA. Therapeutic drug monitoring: which drugs, why, when and how to do it. Aust Prescr 2008;31:42–4.
5. Gross A. Best practice in therapeutic drug monitoring. Br J Clin Pharmacol 2001;52:5–10S.
6. Rossi S, editor. Australian Medicines Handbook. Adelaide: Australian Medicines Handbook Pty Ltd, 2012.
7. Begg EJ. Instant clinical pharmacology. 1st edn. Victoria: Blackwell Publishing, 2003.
8. Baxter K, editor. Stockley's drug interactions: a source book of interactions,their mechanisms, clinical importance and management. 9th edn. Pharmaceutical Press, 2010.
9. eTG complete. Therapeutic Guidelines Limited. Available at https://online-tg-org-au.cknservices.dotsec.com/ip/ [Accessed 6 August 2012].
10. Eadie MJ. Therapeutic drug monitoring – antiepileptic drugs. Br J Clin Pharmacol 2001;52:11–20S.
11. Tomson T, Dahl ML, Kimland E. Therapeutic monitoring of antiepileptic drugs for epilepsy (review). The Cochrane Collaboration 2010;1–16.
12. Campbell TJ, Williams KM. Therapeutic drug monitoring: antiarrhythmic drugs. Br J Clin Pharmacol 2001;52:21–34S.
13. Rogers NM, Jones TE, Morris RG. Frequently discordant results from therapeutic drug monitoring for digoxin: clinical confusion for the prescriber. Intern Med J 2010;40:52–6.
14. Morris R, Frewin D, Saccoia N, Goldsworthy W, Jeffries W, McPhee A. Interference from digoxin-like immunoreactive substance(s) in commercial digoxin kit assay methods. Eur J Clin Pharmacol 1990;39:359–63.
15. Steimer W, Muller C, Eber B. Digoxin assays: frequent, substantial, and potentially dangerous interference by spironolactone, canrenone, and other steroids. Clin Chem 2002;48:507–16.
16. Dasgupta A, Wu S, Actor J, Olsen M, Well A, Datta P. Significant variation. Am J Clin Pathol 2003;119:298–303.
17. MIMS Online, 2012. Available at www-mimsonline-com-au.ckinservices.dotsec.com/Search/Search.aspx [Accessed 6 August 2012].
18. Amdisen A. Clinical features and management of lithium poisoning. Med Toxicol 1988;3:18–32.

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