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Common Sense Pathology

A REGULAR CASE-BASED SERIES ON PRACTICAL PATHOLOGY FOR GPs

CONTENTS

- Measuring drug concentrations
- Avoiding toxicity
- Case studies



Therapeutic drug monitoring

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Therapeutic drug monitoring

Dr Julia M Potter
Dr Peter Collignon and
Dr Peter E Hickman

ANU Medical School, Canberra, ACT.
ACT Pathology, The Canberra Hospital,
Woden, ACT.



INTRODUCTION

Therapeutic drug monitoring is not simply therapeutic drug measurement, but a tool to help in drug dosing, optimise efficacy of therapy and minimise toxicity. In 1997, an International Federation of Clinical Chemistry working group included both plasma drug concentration and the response of the targeted end-organ in the definition of therapeutic drug monitoring.

Measuring plasma concentration is best used for those drugs with a low therapeutic index, that is, where the therapeutic range is not very wide, and where significant side effects occur close to this range. Most importantly, it is useful where it is difficult to predict the appropriate dose for an individual patient. Laboratory measurements of drug concentrations are of particular value when under-dosing and/or over-dosing has potential organ threatening or even fatal consequences.

It should be noted that many available drug assays are not routinely used in general practice because the concentrations do not alter patient management.

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Tower 2, 475 Victoria Ave, Locked Bag 2999
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Ph: (02) 9422 2999 Fax: (02) 9422 2800
E-mail: mail@australiandoctor.com.au
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www.rcpa.edu.au
CEO Dr Debra Graves
E-mail: debrag@rcpa.edu.au

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Common Sense Pathology editor: Dr Matthew Meerkin
E-mail: mmeerkin@ozemail.com.au

Chief sub-editor: Katie Delaney
E-mail: katie.delaney@reedbusiness.com.au

Australian Doctor
Editor: Nadine Meehan
E-mail: nadine.meehan@reedbusiness.com.au

Medical editor: Dr Kerri Parnell
E-mail: kerri.parnell@reedbusiness.com.au

Sales: Suzanne Coutinho and Tim Young
E-mail: suzanne.coutinho@reedbusiness.com.au;
tim.young@reedbusiness.com.au

Graphic designer: Edison Bartolome
E-mail: edison.bartolome@reedbusiness.com.au

Production manager: Katie Randall
E-mail: katie.randall@reedbusiness.com.au

Cover: Photonica/photolibrary.com

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The more common drugs for which determination of in vivo concentration may be of value are listed in Table 1. For these drugs, there is marked inter-person variability of the drug's pharmacokinetics. There also may be significant variations in an individual patient because of variables associated with the disease state (eg, changes in renal function, liver metabolism) as well as a danger from failed or over-enthusiastic therapy.

Table 1: Drugs for which therapeutic drug measurement is generally recommended

Therapeutic groups	Sample collection	Therapeutic range (RCPA Manual)	Modifying influences and potential interactions
Anticonvulsants (see Footnote 1)			
Phenytoin	Trough/pre-dose:	10-20mg/L 40-80µmol/L	Albumin concentration, liver function, drug interactions, synergistic with carbamazepine. As for phenytoin. In addition, an active metabolite, which is not routinely assayed, may result in clinical toxicity with carbamazepine concentration in therapeutic range.
Carbamazepine	If slow release (SR) formulation, pre-dose testing not as important	6-12 mg/L 20-40µmol/L	
Cardio-active			
Digoxin	Anti-arrhythmic (ECG) relationship at six hours post dose. Commonly 12 hours or pre-dose	0.5-1.8µg/L 0.6-2.3nmol/L (Footnote 2).	Renal function (measure creatinine), plasma potassium concentration.
Antibiotics			
Gentamicin and other aminoglycosides	With once per day dosing, measure in 6-14 hour window post dose.	Use nomogram (see Figure 2, pg 7)	Renal function.
Vancomycin	Pre-dose to ensure above known MIC	10-20mg/L	Renal function.
Psycho-active			
Lithium	Trough, pre-dose	0.6-1.2mmol/L	Plasma electrolytes.
Valproic acid	Trough, pre-dose	50-100mg/L 35-700µmol/L	
Clozapine	Trough, pre-dose	400-800µg/L	
Immunosuppressants and cytotoxics			
Cyclosporine	Trough or two hours post dose (Footnote 3)	Dependent on organ and time after transplant.	Interactions change bioavailability (eg, erythromycin, grape fruit juice, St John's Wort). Renal toxicity enhanced by other nephrotoxic drugs (eg, gentamicin).
Endocrine			
Thyroxine	TSH	0.4-5.0mIU/L	See Table 2.
Testosterone	Testosterone	8-35nmol/L	See Table 2 (range for adult male).

Footnotes

1. Other anticonvulsants, such as gabapentin, are not monitored because their effects are not directly related to pharmacokinetic and measurable variables (see Table 2).
2. This is the traditional quoted therapeutic range. See discussion for clarification. Recent recommendations support target concentration of 1.3nmol/L (1.0 mg/L).
3. Dependent on organ transplant type and guided by specialist unit (eg, six months post transplant, trough concentrations for kidney transplant 100-200µg/L, heart transplant 250-350µg/L, liver transplant 170-240µg/L). Some transplant units advocate post-dose monitoring (2 hours), and these concentrations will be much higher. These specialist units will provide appropriate guidelines.



Table 2 includes drugs that are primarily monitored by their end-organ effects in regard to response or toxicity. For example, taking the pulse or measuring blood pressure may indicate a response to beta blockers, and a full blood count may be a measure of toxicity in patients taking azathioprine or 6-mercaptopurine.

Table 2: Therapeutic drug monitoring using clinical (organ) response (pharmacodynamic monitoring)

Therapeutic group	Clinical measure of response
Anticonvulsants	
Gabapentin	Frequency of fitting.
Cardiovascular	
Antihypertensives, beta-blockers Anti-arrhythmics	Blood pressure, pulse rate. Pulse, BP, ECG.
Endocrine	
Hormone replacement therapy	Symptom relief.
	Laboratory-based measurement
Endocrine	
Testosterone	Plasma testosterone concentration, but clinical assessment of adequacy also essential.
Thyroxine replacement Insulin	TSH (sometimes fT4, fT3). Plasma glucose, HbA1c.
Anticoagulants	
Warfarin Heparin	Prothrombin Time (PTT), INR. APTT.
Cardiovascular	
Lipid-lowering drugs (eg, simvastatin)	Creatine kinase (CK), liver function tests (LFT).
Immunosuppressants and cytotoxics	
Azathioprine or 6-mercaptopurine	Full blood count.
Psycho-active	
Clozapine	Full blood count. If patient becomes unwell with flu-like illness, consider troponin measurement.

Case one

Joe is 72. He has a history of AF, which has been responsive to digoxin until recently (62.5µg nocte). He presents feeling unwell and short of breath, complaining of the hot weather. On examination, he looks unwell. His pulse is 90bpm and is very irregular. Other clinical signs are consistent with cardiac failure. Results of laboratory investigations are as follows:

Plasma concentrations (reference/therapeutic intervals)	Potassium 3.4-4.5mmol/L	Creatinine 0.06-0.12mmol/L 60-120µmol/L	Digoxin 0.5-1.0µg/L* 0.6-1.3nmol/L
On presentation	4.5	0.15	2.8µg/L
Previously	3.5	0.11	1.5µg/L

* See digoxin comment below about appropriate reference ranges.

Discussion

- Digoxin is excreted primarily by renal glomerular filtration. The half-life in patients with normal renal function is about 36 hours. The creatinine increase in this man reflects a significant deterioration in renal function, perhaps caused by dehydration in the hot weather.
- As well as causing a decrease in creatinine clearance, diminished renal perfusion results in decreased digoxin clearance and increased plasma half-life. The potassium concentration is important in a patient taking digoxin because of the mechanism of action of digoxin: there is competition between digoxin and potassium for Na⁺-K⁺-ATPase on the outer membrane of cardiac cells.
- The time of measurement of digoxin is important because the best correlation of the neurophysiological response (slowing of the transmission of the action potential through cardiac tissue) and digoxin concentration is six hours post-dose. With the long half-life of digoxin, the plasma concentration will still be clinically useful between six and

- 24 hours (pre-dose), but it is best to be consistent with the time of sampling in a patient if possible.
- The clinical alternatives are either to reduce Joe's dose or briefly stop digoxin therapy. Because the half-life of digoxin in this case would be greater than 36 hours, missing a dose and recommencing at a reduced dose may be appropriate.
 - Follow-up measurement of plasma digoxin and reassessment of creatinine and potassium status would be appropriate 10 days after recommencing therapy because steady-state is attained after about five half-lives (in Joe's case allowing an arbitrary increase in half-life to about two days). With the return of cooler weather and an expected improvement in renal function, Joe may need close monitoring to ensure his serum digoxin level does not become sub-therapeutic.
 - Research suggests that adverse outcomes may be associated with digoxin concentrations in the upper half of the traditional therapeutic range (0.5-1.8µg/L). However, it is difficult to assess how much electrolyte imbalance and poor renal function contribute to this. The message is that in patients taking multiple cardioactive drugs (eg, ACE inhibitors and/or beta-blockers), it is desirable to aim for a trough concentration around 1µg/L, and concomitant monitoring of electrolytes and renal function is mandatory.

Cases two and three

Jane, 35, has a history of chronic renal failure and epilepsy. She has been on a stable dose of phenytoin for five years and has had no recent fits. Her plasma phenytoin concentration is 32µmol/L (8mg/L) with the sample collected immediately pre-dose. The therapeutic range is 40-80µmol/L or 10-20mg/L. Should the dose be increased?

Jenny is also 35, but has a history of drug use, hepatitis C and epilepsy, which has been difficult to control. She recently presented fitting to the local hospital's emergency department. The plasma phenytoin concentration was 20µmol/L (5mg/L). The dose of phenytoin was increased from 300mg a day to 400mg a day at that time. Two weeks later, she presents to her local doctor with ataxia. How should she be managed?

Jane and Jenny represent some of the contrasts in the use of phenytoin, which is highly protein bound, with 10% free in plasma when the albumin concentration is normal. It is metabolised primarily in the liver, although to a degree that varies widely between patients. The enzymatic pathway can also be saturated at normal therapeutic doses. Therefore there is not a predictable proportional (first order) increase in plasma concentration as the dose is increased.

In Jane's case, the important clinical information was that her epilepsy was controlled, even with the concentration below the therapeutic range. However, the missing laboratory information is that her plasma albumin concentration was 30g/L (reference range 35-50g/L). Because the concentration of binding protein was reduced, there was a proportional increase in the free phenytoin concentration, which is the pharmacologically active moiety. (In practice, the measurement of free phenytoin is complex and usually adds little to clinical management.)

By contrast, Jenny's phenytoin concentration when she was seen in the surgery had increased to 112µmol/L (28mg/L). Other investigations showed plasma albumin of 38g/L and gamma glutamyl transferase (GGT) of 240U/L (reference range <30u/L). The ataxia reflects the cerebellar toxicity of phenytoin, which is related to the plasma concentration. A dose reduction is clearly in order. In addition, Jenny had previously been non-compliant with therapy, and her becoming more compliant also contributed to the toxic level.

In Jenny's case, the pathway for phenytoin metabolism is saturated, so its half-life will be longer than the usual 24 hours. Therefore, it is not possible to accurately calculate the time it would take to achieve a new steady state after dose reduction and any decrease in plasma concentration would only occur after the excess drug had been metabolised.

If Jenny missed some doses, this lag period would be shorter, but it may give an undesirable message to her about the acceptability of missing doses. In the absence of any other signs of biliary stasis, the raised GGT may be a reflection of phenytoin-induced hepatic enzyme induction — enough to shorten the drug's half-life when the drug's pathway is not saturated, but not enough to cope with a 33% increase in dose. Whichever dose reduction regime is selected, re-assay performed seven days after either reduction of dose (or cessation followed by reintroduction) would give useful information. In people on a single anticonvulsant, a sudden reduction in dose has the potential to precipitate a loss of therapeutic control and subsequent fits.



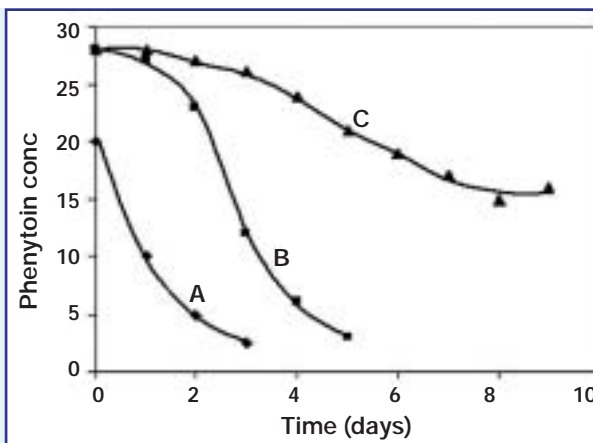


Figure 1.

A. Comparisons of changes in phenytoin concentrations with time. Plasma concentration falls with half-life of about 24 hours after dose ceased.

B. There is an apparent delay in the plasma half-life falling in this patient after stopping the phenytoin. In this case, the enzyme pathway is saturated, and a significant fall is not seen immediately. The final clearance half-life is the same as in A.

C. In this case, in the presence of sustained but reduced administration of phenytoin, the amount being administered each day is only slightly less than the capacity of the pathway. Hence the rate at which the concentration falls is slow, and symptoms of toxicity will continue while the concentration is elevated. If the dose decrease had still exceeded the capacity, then the concentration would have increased (not shown).



Case four

Godfrey is a frail 80-year-old. He has had a hip replacement after a fractured neck of femur and post-operatively develops a urinary tract infection for which he is given gentamicin 240mg once daily. Post-operatively, he is difficult to mobilise and now complains that he can't hear what anybody is saying. Laboratory results are shown summarised below.

Day	Day 1 (1st dose)	Day 10	Day 20
Plasma creatinine (0.06-0.12mmol/L)	0.11	0.30	0.15
Plasma gentamicin (24 hours post infusion)	1.5mg/L	6mg/L	-

Discussion

Gentamicin is the most commonly used aminoglycoside, a family of drugs notorious for its nephrotoxicity. Less well recognised is the potential for ototoxicity caused by some drugs in this class.

Aminoglycosides are cleared through the kidney by glomerular filtration. In the past decade, the administration of these antibiotics has changed to once daily dosing for most adults, even though the plasma half-life is short in those with normal renal function. If aminoglycosides are given more frequently with lower peak concentrations, their efficacy in terms of percentage of bacteria killed decreases (ie, there is a period of relative post-antibiotic resistance). So the net effect of once-daily dosing is greater than that of thrice daily dosing.

The recommended measures for monitoring patients on gentamicin are plasma aminoglycoside concentration and creatinine concentration, given that renal toxicity is a major end-organ effect. With once daily dosing, the time of collection of the sample for aminoglycoside monitoring is 6-14 hours after administration. The serum aminoglycoside concentration is compared with a nomogram, which gives the target concentration with maximum and minimum concentrations for the known time of collection (see Figure 2, below). If the nomogram is not readily available, a compromise is for the laboratory to quote a sequence of ranges according to time to allow interpretation (eg, target \pm range for 6, 10 and 14 hours).

In Godfrey's case there were several errors that resulted in his developing renal toxicity and ototoxicity. He showed evidence of recovery from the renal damage (ie, creatinine has fallen on day 20), but ataxia and deafness are often permanent.

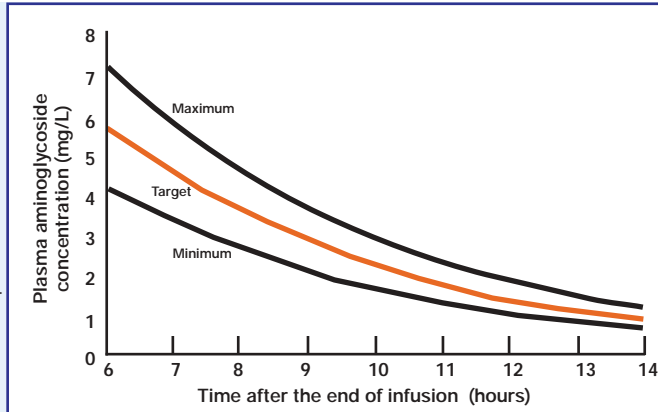
There were two problems in the monitoring of Godfrey's aminoglycoside therapy. First, the dose of gentamicin was too high for this elderly man whose plasma creatinine of 0.11mmol/L with a small muscle mass suggests the presence of renal impairment. Second, while the high gentamicin dose could potentially have been identified after the first dose of gentamicin, the monitoring that was undertaken was, at 24 hours post dose, inappropriate. A serum concentration of 1.5mg/L may be appropriate with a three times daily dosing, but is too high for once-daily dosing.

If prompt attention had been given to Godfrey's difficulty walking and hearing loss, and further plasma creatinine measurements made, gentamicin toxicity would have been apparent earlier and the agent ceased.

Figure 2.

Nomogram of gentamicin concentrations with time after infusion. Ideal monitoring during once per day dosing should be undertaken with sample collection between six and 14 hours after completion of the infusion (over 30 minutes). The target concentration is identified and the dose should be adjusted if the concentration falls outside the intervals shown for that time point. Laboratories may report results giving selected time points: for instance

Six hours post infusion: recommended	4-7mg/L
10 hours	1.5-3mg/L
14 hours	0.8-1.2mg/L



Case five

Alan, 40, has bipolar disorder, which is controlled on lithium (slow-release preparation, 450mg bd). He presents to the surgery feeling tired, weak, shaky and complaining of nausea. Your first thought is that he has flu and has been overdoing things. The plasma lithium concentration result is available the next morning and is 1.6mmol/L (therapeutic range for chronic maintenance 0.6-1.2mmol/L). The comment on the report draws your attention to the time of the last dose and of sample collection, stating it to be about eight hours post dose. The previous lithium concentration 12 months earlier was 0.8mmol/L.

You wonder about the possible explanations for an increase of Alan's lithium concentration into the toxic range. What medical causes might result in this change? A review of his medications shows no obvious candidates for a drug interaction. Further questioning reveals that to lose weight, Alan has taken up jogging every morning, with predictable aches and pains in muscles and joints. In response, he has been taking ibuprofen bought from the local supermarket.

Is the ibuprofen significant in this case?

Quite possibly. NSAIDs may have significant effects on renal function. They increase the resorption of lithium in the proximal tubule, decreasing its clearance and increasing its plasma concentration. This is exacerbated in patients who are dehydrated or have other causes of renal impairment. In addition, lithium itself may cause renal tubular damage.

This case shows the importance of obtaining a complete medication history including OTC preparations or complementary medicines (eg, Table 1, cyclosporine).

Comment

The recommended time for sample collection for lithium is immediately pre-dose (trough). However, if a slow-release formulation is being used, as in this case, it is acceptable to sample earlier in the dosing interval, because the absorption kinetics of the preparation are designed to eliminate the wide swings in plasma concentration. If patients on any slow-release preparation develop symptoms towards the end of the dosing interval, it needs to be determined whether the concentration is sub-therapeutic at that time. This is really no different to timing principles used with standard preparations. The converse is that if a patient has symptoms of toxicity only occurring post dose then it may be caused by high peak concentrations, possibly because of rapid absorption. In both cases it would be reasonable to collect samples at the time of the symptoms, indicating the reason to the laboratory.

Conclusion

Therapeutic drug monitoring is the assessment of efficacy and/or toxicity, knowing likely risks, by means of direct drug measurement and/or indirect assessment of target organ responses. In assessing drug efficacy and toxicity, it is necessary to know the target organs for the drug, other organs, that might be affected by the drug and other conditions that may potentiate toxicity, such as hypokalaemia and renal failure. A measurement of drug concentration should never be interpreted in isolation. In the case of gentamicin, target organ toxicity with deteriorating renal function is an additional guide to problems as well as its plasma concentration.



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Acknowledgment:
We thank Therapeutic Guidelines for its kind permission to reproduce the figure, Aminoglycoside plasma concentration versus time for once-daily dosing, as shown in *Therapeutic Guidelines: Antibiotic, Version 12*.

Further reading
Australian Medicines Handbook, 5th edition. Australian Medicines Handbook Pty Ltd, Adelaide.