Practical considerations for Therapeutic Drug Monitoring

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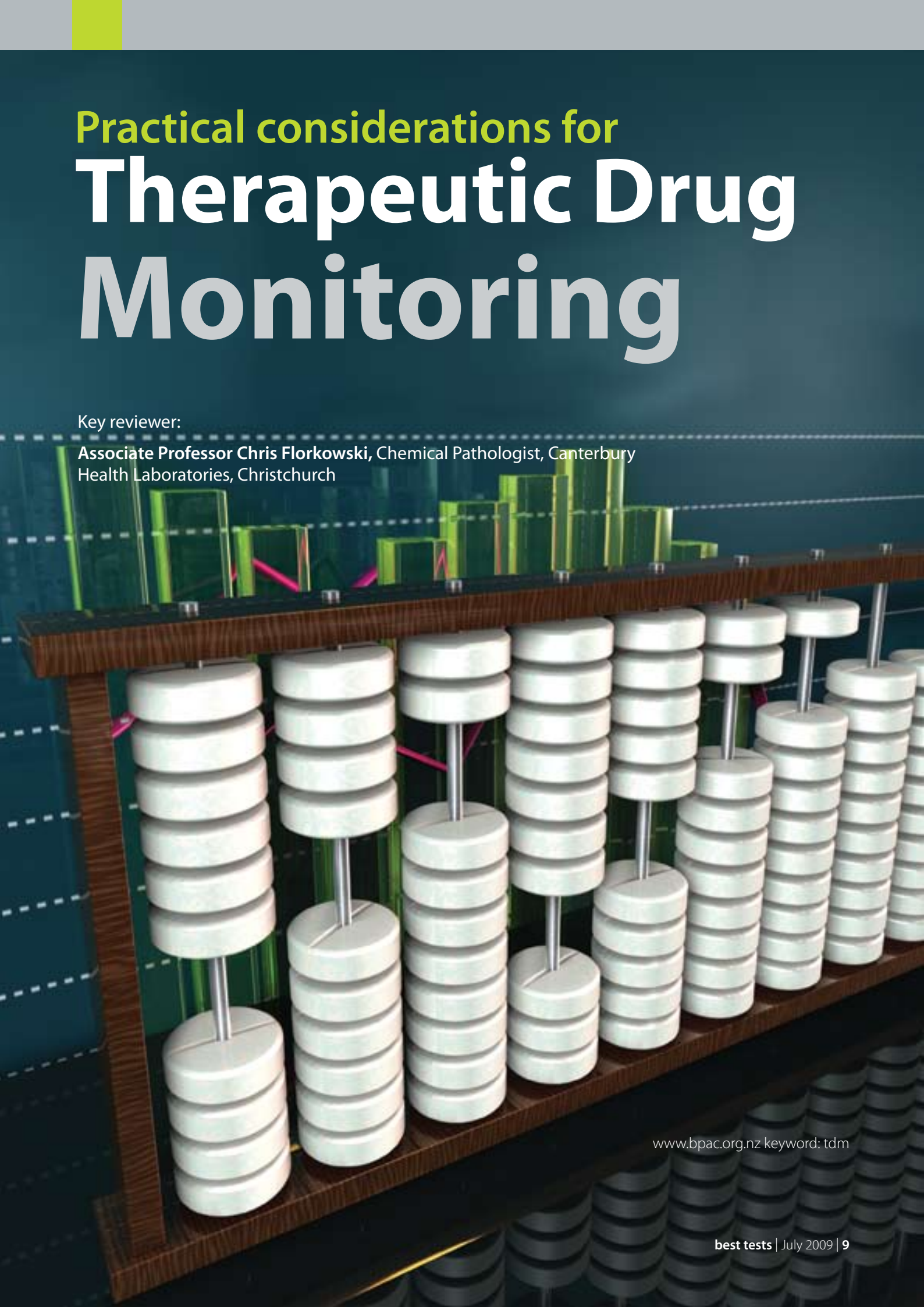

www.bpac.org.nz keyword: tdm

Therapeutic drug monitoring (TDM) is the measurement of the concentration of specific drugs at intervals in order to adjust dosage regimens to achieve a desired clinical effect and avoid toxic effects.

TDM is used where:

1. There is an established relationship between blood drug concentration and therapeutic response and/or toxicity
2. There is a poor relationship between blood drug concentration and drug dosage
3. There are clear clinical indications for the test (such as: no response to treatment; suspected non-compliance; signs of toxicity)
4. The specimen can be provided, appropriately timed and dated, with identifiable patient information
5. Adequate clinical information is supplied to allow the interpretation of results

In order to get meaningful results when undertaking therapeutic drug monitoring, the following needs to occur:

- All dosing and collection time details should be included on the request from (see Table 1)
- Samples should not be collected until drugs have reached steady state (five half lives) (see Table 2)
- Bloods should be collected at the recommended sampling time (see Table 2)

The timing of blood collection is important

Sample once steady state achieved

In most cases blood samples should not be collected until concentrations have reached steady-state. This occurs when the rate of drug administration and drug elimination are equal, for most drugs this is achieved after 4–5 half-lives. If a loading dose has been administered, steady state may be achieved earlier. Drug concentrations may be determined earlier if toxicity is suspected. It is important to wait for steady-state both at initiation and following any dosage change.

Sample at the appropriate time in relation to last dose

When a drug is administered, it goes through the stages of absorption, distribution, metabolism and elimination. Drug concentrations are generally measured in the elimination phase (correlates with trough) as this gives a more predictable and reliable guide to drug dosing.

Different drugs have variable pharmacokinetic characteristics, for instance, digoxin and lithium have extended distribution phases following dosing. This means, that if blood is taken too soon after administration, the level will appear to be elevated.

Details to include on the request form

To accurately interpret results, it is important the request form contains all relevant information. See Table 1.

It can be difficult to make sense of a result unless collection time and previous last dose is known. For example, drug levels that are in the toxic range may have been taken only a few hours post dose, and therefore the drug was still in its distribution phase.

It is important to note how long the person has been on the drug, to ascertain they have achieved steady-state. If there are any known issues with compliance, include on the form.

It is also useful to include on the request form any co-morbidities or other medications, as these may effect the drug pharmacokinetics. For example, steady-state for digoxin is 5–7 days, but may take up to three weeks in a person with renal failure.

Table 1: Information required on request form[1]

Time sample collected
Time dose given
Dosage regimen (dose, duration, dosage form)
Patient demographics (age/sex)
Other medications
Other relevant co-morbidities (e.g. renal/liver disease)
Indications for testing (e.g. ? toxicity, non-compliance)

Table 2: Recommended sampling times[2, 3]

	Time to steady state	Recommended sampling time	Half-life	Note
Carbamazepine	14 days	Immediately pre dose	10–20 hours	Reduced clearance can occur in children, after chronic therapy and with other anti-convulsants.
Digoxin	7 days	6–24 hours post dose	36 hours	In renal failure, may take up to 3 weeks to reach steady state. Routine monitoring not recommended.
Lithium	5 days	12 hours post dose or Immediately pre dose	10–35 hours	Reduced clearance in children. Decreased renal function may lead to increased concentration, especially in the elderly. Drug accumulation is enhanced by dehydration.
Phenytoin	14 days	Immediately pre dose	6–24 hours	Time to steady state may depend on dose. Altered clearance when taken with other anticonvulsants.
Theophylline	2 days	2–4 hours post dose	4–16 hours	Prolonged clearance in neonates, reduced clearance in children. Prolonged clearance in severe illness notably respiratory failure and CHF.
Valproate	3 days	Immediately pre dose	11–17 hours	Reduced clearance when taken with enzyme inducers e.g. phenobarbitone, phenytoin. There is poor correlation between valproate levels and clinical effect. The main reason for measurement is to assess compliance.

References

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3. Kyle C (Ed), A Handbook for the Interpretation of Laboratory tests. 4th Edition, 2008, Diagnostic Medlab.