Why do therapeutic drug monitoring

In this third article in our back to basics series on pharmacokinetics, Alison Thomson gives an overview of the factors that make therapeutic drug monitoring necessary and looks at some of the groups of drugs where monitoring is often needed.

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**Identify knowledge gaps**

1. List five drugs that need therapeutic monitoring.
2. What factors affect the time at which a blood sample should be taken for measuring drug levels?
3. Why are some hospitals using gentamicin regimens with high doses at longer intervals?

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**When to collect a sample**

Drug concentrations are usually measured in whole blood or serum, although saliva, which gives a measure of the unbound drug concentration, may be a useful alternative when blood samples are difficult to collect. For example, measuring phenytoin concentrations in children.

Unlike most sampling for biochemistry and haematology, the timing of the sample (in relation to the previous dose) influences the interpretation of a drug concentration measurement. For most drugs, the relationship between response and concentration (and, therefore, target concentrations) is based on steady-state samples (see PJ, 19 June, p769) taken at specific times after the dose. "Trough" concentrations (at the end of the dosage interval) are commonly used for anti-inflammatory and anti-convulsant drugs, whereas "peak" concentration measurements may be useful for some antibiotics. The relationship between concentration and response is sometimes determined by the time above a threshold value (for example, the minimum inhibitory concentration [MIC]).

Responses to some anticancer drugs and immunosuppressants have been related to the patient's overall exposure to the drug, as measured by the area under the concentration–time curve (AUC). The AUC takes into account both the dose and the patient's ability to clear the drug. So:

$$\text{AUC} = \text{dose} \times \text{clearance}$$

Figure 1 illustrates that, despite being given the same dose, a patient whose clearance is 4L/h has an overall exposure to the drug that is twice that of a patient whose clearance is 8L/h. Note, however, that in this case their trough concentration measurements are similar. This means that if only trough samples are taken, both patients would appear to have the same dosage requirements. Similar problems occur when there is wide variability in bioavailability.

**Anti-infective agents**

Many anti-infective agents have a wide therapeutic range, which means that standard doses can be used. However, with some antibiotics (eg, gentamicin), toxicity is associated with persistently high concentrations whereas with others (eg, vancomycin), treatment failure can result from persistently low concentrations. Antibiotics are often classed as "time-dependent", where the aim is to maintain concentrations above the MIC for most of the dosage interval or as "concentration-dependent", where the aim is to achieve high peak concentrations but allow the concentration to fall to low levels between doses.

**Aminoglycoside antibiotics**

Aminoglycosides have concentration-dependent activity against gram-negative organisms. The higher the peak, the faster the kill rate. Clinical efficacy has been related to the ratio of the peak concentration to the MIC. A ratio of 8 to 10 (ie, concentrations around 10mg/L) is the most effective for gentamicin. Since traditional doses of 1.5mg/kg eight hourly rarely achieve adequate peaks but often produce excessive troughs, some hospitals have started using higher doses at 12 to 24 hour intervals.
while others use single doses of 5–7mg/kg with extended intervals of 24 to 48 hours. These changes have presented analytical challenges in the monitoring of aminoglycoside therapy because the peaks and troughs attained can be in ranges associated with high assay variability.

Many hospitals still measure peak and trough concentrations but aim for peaks above 7mg/L for gram-negative septicemia rather than the traditional 5 to 10mg/L range. Concentrations less than 2mg/L remain the target for the trough although with 12 to 24 hourly dosing, troughs often fall below 1mg/L. Table 1 shows sampling times and a range of target concentration ranges for various anti-infective agents.

When doses of 5–7mg/kg are used, peak concentrations are usually above 10mg/L and require dilution while troughs are either below the detection limit or at a level where precision is poor. Samples are, therefore, often taken six to 14 hours after the dose, when the measurement is normally within a range that has acceptable precision. The result is then plotted on a nomogram, such as a Hartford nomogram. This tool uses the sampling time and drug concentration measurement to determine whether the dosage interval needs to be increased.

Glycopeptide antibiotics In contrast with the aminoglycosides, the glycopeptide antibiotics, vancomycin and teicoplanin exhibit time-dependent activity and the aim is, therefore, to achieve a flat profile that maintains concentrations above the MIC. In the past, both peak and trough concentrations of vancomycin were monitored but there was little agreement on either the timing or the target range of peak concentrations. Trough concentrations of 2 to 10mg/L (ie, at least two to four times the MIC) are usually considered adequate but up to 15mg/L may be required for some serious infections. Some hospitals use constant rate infusions of vancomycin, aiming to maintain concentrations between 15 and 25mg/L.

Teicoplanin concentrations are not measured routinely but this can be useful if under-dosing is suspected, especially if the infection is severe or deep-seated. Target troughs vary according to the condition being treated.

Antitubercular drugs Low concentrations of rifampicin have been associated with treatment failure and although unreliable adherence is often blamed, poor absorption may also be a factor. Monitoring concentrations can help to clarify these issues and identify patients who need higher doses. Rifampicin has a short elimination-half life so trough concentrations are undetectable and peak concentrations measured two hours after the dose are normally used. However, because the rate of absorption is slow in some patients, the peak may occur later than this and an additional sample six hours after the dose may be useful. Other antitubercular drugs that can be monitored include cycloserine, isoniazid, rifabutin, pyrazinamide and streptomycin.

Antifungal drugs Amphotericin concentrations are rarely measured but peak concentrations of flucytosine above 100mg/L have been associated with neurotoxicity and treatment failure is a possibility if trough concentrations drop below 25mg/L. There is some evidence that trough concentrations of itraconazole above 0.5mg/L are desirable so monitoring of this drug could become more common.

Antiretroviral drugs Unexplained treatment failures and a high incidence of drug interactions have led to an interest in the monitoring of antiretroviral drug concentrations. The protease inhibitors (eg, saquinavir, neflavinav, ritonavir, indinavir) have received particular attention because of their complex and variable pharmacokinetics and the recognised association between trough plasma concentrations and virological response. Other parameters that are currently under investigation include using the inhibitory quotient (ratio of the trough concentration to the IC50 — the drug concentration that inhibits replication in 50 per cent of the virus isolate) and resistance testing to guide decisions about which drugs to use and at what dose.

The role of therapeutic drug monitoring for non-nucleoside reverse transcriptase inhibitors (eg, zidovudine, lamivudine) because their effects depend on the intracellular concentrations of triphosphate anabolites rather than the plasma concentrations of the parent drug.

Immunosuppressants Ciclosporin blocks the replication of lymphocytes and inhibits the release and production of interleukin–2. It plays an important role in a range of clinical conditions, including organ transplantation. It has long been recognised that low ciclosporin concentrations can increase the chance of graft rejection while high concentrations are associated with nephrotoxicity. Therefore, therapeutic drug monitoring is advisable. However, ciclosporin is difficult to measure and early immunoassays detected both parent drug and a range of metabolites, leading to wide variability in proposed target ranges. Current assay methods are more specific and the focus has changed from analytical issues to the relationships between pharmacokinetic parameters (eg, AUC) and response.

Initial studies focused on trough concentration measurements but this is a relatively insensitive indicator of the patient’s exposure to ciclosporin because of the wide variability in oral bioavailability. There is a closer relationship between AUC and response than with trough concentration and response.

Table 1: Sampling times and target concentration ranges for a range of antimicrobials

<table>
<thead>
<tr>
<th>Drug</th>
<th>Time after dose (hours)</th>
<th>Target Range (mg/L)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antibiotics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gentamicin</td>
<td>1</td>
<td>5–10</td>
<td>&gt;7mg/L for serious infections</td>
</tr>
<tr>
<td></td>
<td>trough</td>
<td>&lt;2</td>
<td>Nomogram used</td>
</tr>
<tr>
<td></td>
<td>6–14</td>
<td>not applicable</td>
<td></td>
</tr>
<tr>
<td>Amikacin</td>
<td>1</td>
<td>20–30</td>
<td></td>
</tr>
<tr>
<td></td>
<td>trough</td>
<td>&lt;10</td>
<td>&lt;5mg/L used in some centres</td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>trough</td>
<td>10–20</td>
<td>&gt;20mg/L (&lt;60mg/L) for deep-seated infections</td>
</tr>
<tr>
<td>Vancocycin</td>
<td>trough, steady state</td>
<td>5–10</td>
<td>5–15mg/L used in some hospitals</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15–25</td>
<td>Constant rate infusion</td>
</tr>
<tr>
<td><strong>Antitubercular agents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cycloserine</td>
<td>2</td>
<td>20–35</td>
<td></td>
</tr>
<tr>
<td></td>
<td>trough</td>
<td>10–20</td>
<td></td>
</tr>
<tr>
<td>Ethambutol</td>
<td>2–3</td>
<td>2–6</td>
<td></td>
</tr>
<tr>
<td>Rifampicin</td>
<td>2 and 6</td>
<td>8–24</td>
<td>Absorption delayed in some patients</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>1, 2, 4 and trough</td>
<td>0.3–9</td>
<td>Target peak, absorption rate variable</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>2 and 6</td>
<td>3–6</td>
<td>Daily dose</td>
</tr>
<tr>
<td></td>
<td>2 and 6</td>
<td>9–18</td>
<td>Twice weekly dose</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>2 and 6</td>
<td>20–50</td>
<td>Daily dose</td>
</tr>
<tr>
<td></td>
<td>2 and 6</td>
<td>40–100</td>
<td>Twice weekly dose</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>1</td>
<td>35–45</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

"Trough" means end of the dosage interval (ie, 12 hours after the dose for 12-hourly dosing and 24 hours for 24-hourly dosing)
which has led to the use of absorption pro-
filng using three or four samples or a single
two hour post dose (“C2”) sample as a sur-
rrogate for AUC. Clinical outcomes have
improved when doses are adjusted on the
basis of C2 rather than trough measure-
ments.

Tacrolimus has many of the analytical dif-
ficulties associated with ciclosporin and it also
has a low bioavailability. However, there is a
more consistent relationship between trough
concentration and AUC, so therapy is usually
based on trough measurements. Relationships
have also been identified between response
and concentrations of the newer immuno-
suppressants, sirolimus, mycophenolic acid
and everolimus, but analysis of these drugs
currently requires assay techniques that are
not generally available in routine clinical lab-
oratories.

Antiepileptic drugs
Monitoring concentrations of antiepileptic
drugs became popular during the 1980s
when it was recognised that it could help to
reduce variability in response and toxicity.
Most of the older anticonvulsants are elimi-
nated by hepatic metabolism, leading to a
wide range of dose requirements and a high
incidence of drug interactions. However, as
experience with the traditional anticonvul-
sants developed, it became clear that other
factors, such as the active metabolite of carba-
mazepine and the concentration–dependent
protein binding of valproic acid, limited the
value of routine analyses. Currently, valproic
acid is rarely analysed, carbamazepine con-
centrations are occasionally monitored and
phenobarbital is rarely used.

Phenytin monitoring remains useful be-
cause its non-linear pharmacokinetics make
dose adjustment difficult. However, care is
required in patients with low albumin or
renal failure because the consequent reduc-
tion in plasma protein binding can lead to
misinterpretation of total (free and bound)
conzentration measurements. In such cases,
the result can be normalised by using a
correction factor.

The newer anticonvulsants have wider
therapeutic indices, so the monitoring of
drug concentrations is rarely performed in
practice. Nevertheless, a tentative target range
of 3–14mg/L (12–55µmol/L) has been pro-
posed for lamotrigine.

Drugs used in psychiatry
Target ranges have been identified for a num-
ber of antidepressants and antipsychotics,
many of which are metabolised by cytochrome P450 2D6, an isoenzyme with
variable activity due to genetic polymor-
phism. Significant differences in dosage
requirements have been demonstrated be-
tween poor metabolisers and extensive
metabolisers and, although rare, ultrarapid
metabolisers have been identified who have
unusually high dosage requirements.

Previously, such patients were assumed to
have poor adherence because they had low
concentrations relative to the prescribed dose.
However, with the possible exception of
clozapine, the routine analysis of drugs used
in psychiatry is not common in the UK,
although it is popular in other parts of
Europe.

Lithium Although a valuable drug in the con-
trol of mood disorders, lithium has the disad-
vantge of having a narrow therapeutic range.
It is cleared renally, and mimics the excretion
and reabsorption of sodium in the renal
tubules. Consequently, it accumulates quickly
if renal function alters or if the patient be-
comes dehydrated. It is recommended that
lithium concentrations are checked every
three months and the target range of
0.4–1mmol/L is based on a sample taken 12
hours after a dose.

Anticancer drugs
Although anticancer drugs have narrow ther-
apeutic ranges, concentrations are not
routinely monitored because of a lack of data
on concentration–effect relationships. One
exception, however, is methotrexate, where
folic acid rescue therapy is based on moni-
toring the methotrexate concentration 24–48
hours after high dose therapy and continuing
until concentrations are below 0.05µmol/L.
For other anticancer drugs, monitoring the
enzyme responsible for their metabolism has
been used to help adjust doses and reduce
toxicity of mercaptopurine (thiopurine
methyltransferase activity) and fluorouracil
(dihydropyrimidine activity).

Digoxin
Digoxin is probably the drug that is moni-
tored most frequently in routine clinical prac-
tice but sampling is often inappropriate.
Because digoxin takes a long time to distrib-
ute into its large volume of distribution, sam-
ple taken earlier than this may contain con-
centrations up to three times the average
steady state concentration. This can lead to
misinterpretation of the result and an inap-
propriate dose adjustment. Target concentra-
tion ranges for steady state samples taken
more than six hours after the dose are
0.8–2mg/L (1.2–6µmol/L). Another com-
mon error with digoxin is to ignore the
effects of ageing and changes in renal func-
tion in patients on long-term therapy. These
may not be recognised if patients are receiv-
ing repeat prescriptions over a prolonged
period, resulting in excessive accumulation
and toxicity.

Theophylline
Although theophylline has largely been re-
placed by other drugs with less potential for
adverse effects, it is still used in some patients.
Since it is principally cleared by hepatic me-
tabolism, dosage requirements vary widely
and drug interactions remain a major con-
cern. Bronchodilator effects have been
demonstrated within the normal target range
of 10–20mg/L (55–110µmol/L) but lower
concentrations are associated with anti-in-
flammatory and steroid sparing effects.
Consequently, there is some support for re-
ducing the target range to 5–15mg/L
(28–80µmol/L), which might reduce the
incidence of toxic effects.

Summary
The appropriate use of therapeutic drug
monitoring requires more than simply meas-
uring the concentration of a drug in the
patient’s blood and comparing it with a tar-
gent range. It starts when the drug is first pre-
scribed and involves determining an initial
dosage regimen that is appropriate for the
clinical condition being treated, the patient’s
clinical characteristics (age, weight, renal
function, etc) and concomitant drug therapy.
When interpreting concentration measure-
ments, factors that need to be considered are:
the sampling time in relation to the

dose, the dosage history (ie, whether or not
the result represents steady state), the pa-
ient’s response, and the desired clinical tar-
gets. This information can be used to adjust
doses to achieve the optimal response with
minimum toxicity.

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Correction

Three values in this CPD article should have been expressed in micromoles and not millimoles. The following should have read: “until concentrations are below 0.05µmol/L” (p155, column 2, section on anticancer drugs), “the normal target range of 10–20mg/L (55–110µmol/L)” (p155, column 3, section on theophylline) and “reducing the target range to 5–15mg/L (28–80µmol/L)” (p155, column 3, section on theophylline).