19

Drug Monitoring in Therapeutics

19.1 Introduction

The basic tenet of drug monitoring is that drug therapy is more satisfactorily controlled if patients receive doses adjusted to give optimum plasma concentrations or optimum effects, whichever is the easier to measure. The aim is to provide objective assessments that are more likely to lead to successful therapy than clinical judgment alone. Having said that, many drugs can be used without a need for the kind of monitoring as described in this Chapter. It is those drugs for which the margin between adequate dosage and potentially toxic dosage is small, those that show latent toxicity, and those for which a direct pharmacological response cannot be measured, that should be monitored.

For some drugs it is relatively easy to measure the pharmacological (physiological or biochemical) effects. Examples include:

- Blood glucose for antidiabetic drugs such as insulin and oral hypoglycaemic drugs
- Blood lipids for 'statins' and other hypolipidaemic agents
- Blood pressure for antihypertensive drugs
- Electrocardiogram for antiarrhythmic drugs
- Prothrombin time for anticoagulants such as warfarin.

However, for those drugs for which it is difficult to predict effects from the size of the dose, then measurement of drug concentrations in plasma, or some other suitable fluid, may be appropriate. Thus, the combination of therapeutic drug monitoring (TDM) using chemical assays and the discipline of pharmacokinetics is useful for only a small number of compounds, and generally should not be contemplated unless there is:

- No direct method of measuring the pharmacological effect of the drug
- A poor or non-existent correlation between dose and effect
- A narrow therapeutic window
- Large inter- and intra-individual differences in drug disposition.

Furthermore, TDM requires:

- That there is a correlation between the measured concentration of drug and/or its metabolite(s) and the pharmacological effects of the drug.
- That reliable analytical methods for measuring the drug and/or its active metabolite concentrations in a clinically relevant timeframe, are available.

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Drug concentrations may also be measured to assess compliance (whether the patient is taking the drug as instructed) or to investigate adverse effects, drug–drug interactions, or acute poisoning. An additional objective of monitoring may be to minimize overall long-term exposure consistent with a useful response. The value of TDM is demonstrated most obviously by data on theophylline, phenytoin, gentamicin, digoxin, ciclosporin and lithium.

19.2 General considerations

19.2.1 Samples and sampling

Whole blood, plasma and serum are not the same thing. Plasma and serum are usually suitable for TDM, and, provided that the samples have been collected and stored correctly, there are generally no significant differences in the concentrations of drugs in these two fluids. However, standardization for any particular example is desirable. Traditionally, serum is used for lithium assays to avoid potential contamination by lithium heparin that may be used as the anticoagulant. Blood and plasma concentrations may be markedly different depending on the degree of partitioning into or binding to red cells. When drugs are extensively distributed into erythrocytes, then lysed whole blood (easily achieved by freezing the sample) may be better as even a small degree of haemolysis may significantly elevate plasma concentrations. Whole blood should be used for the immunosuppressants ciclosporin, sirolimus, and tacrolimus because they redistribute between plasma and erythrocytes once the sample has been collected.

Saliva is an ultrafiltrate of plasma with the addition of certain digestive enzymes and other components. There has been interest in the collection of saliva for TDM purposes because collection is non-invasive and salivary analyte concentrations are said to reflect non-protein bound plasma concentrations (Section 3.3.4). However, reliable saliva or oral fluid collection requires a co-operative individual and even then is not without problems. Saliva is a viscous fluid and thus is difficult to pipette. Some drugs, medical conditions, or anxiety, for example, can inhibit saliva secretion and so the specimen may not be available from all individuals at all times. Use of acidic solutions such as dilute citric acid to stimulate salivary flow alters saliva pH and thus may alter the secretion rate of ionizable compounds. Additionally, stimulated saliva flow can result in diluted saliva and hence reduced drug concentrations. Saliva is a useful medium to sample from children, for example those attending epilepsy clinics. Collection is non-invasive and children are less inhibited about spitting into a pot than the majority of adults.

19.2.2 What should be measured?

Generally, the parent drug is measured, or in the case of a prodrug, the active metabolite. Aspirin is rapidly hydrolysed to salicylate *in vivo*, and it is usually salicylate that is measured. For some drugs, an active metabolite may make a significant contribution to the overall clinical and/or toxicological effects. Some TDM protocols advocate using a total value (i.e. parent drug plus active metabolite(s)), others may consider the concentration of metabolite separately. An immunoassay may measure parent drug and metabolite and the result will depend on the relative concentrations of drug and metabolite, and the cross-reactivity of the antibody for the metabolite. This may or may not be an advantage of using immunoassay. Different immunoassays may give different results and this is one of the reasons why clinics, based upon their experience, may define their own reference ranges.

To measure the concentration of an active metabolite as well as that of the parent drug will probably require a chromatographic method. A further advantage of knowing the relative concentrations of drug and metabolite is that they may give an indication of when the sample was taken relative to the time of the last dose of drug. A higher than expected drug/metabolite ratio may indicate that the time between the dose having been taken and the sampling is shorter than the prescribed interval.

19.2.3 Timing of sample collection

Timing of the sample collection is crucial as consideration of typical multiple-dose plasma concentration–time curves (e.g. Figure 4.11) will indicate. There are likely to be major differences between peak and trough concentrations, and published concentrations will usually be based on samples collected at a defined time after the last administered dose. Furthermore, the time at which peak concentrations occur is more difficult to define and may be variable within and between patients. A very common, almost standard TDM guideline is to sample immediately before the next dose, or the following morning after an evening dose ('pre-dose' or 'trough' sample) to allow for absorption and distribution to tissues to be completed before sampling (but see individual examples, later). Trough concentrations are expected to be more repeatable than peak concentrations. Generally, samples are not taken until steady-state conditions have been achieved, approximately five times the elimination half-life. An exception to this 'rule' is carbamazepine which undergoes extensive auto-induction (Section 17.4.1). The recommended delay between initiation of therapy or dosage adjustment is 20 days, to allow for the reduction in half-life and stabilization at a new (lower) steady-state concentration. Also, because phenytoin exhibits dose-dependent kinetics, exceptionally long time intervals are needed after changing the dosing regimen before the next plasma sample is taken. For some drugs, such as immunosuppressants, measurement of the *AUC* is considered a better indicator of overall exposure but this raises practical difficulties with regard to the large numbers of samples that would have to be collected and analysed. Noticing an empirical relationship between the peak concentration and *AUC* of ciclosporin, Jorga *et al*. (2004) suggested that peak (i.e. 2 hour post-dose sampling) is possibly a better indicator of optimal dosage than pre-dose or 4 hour post-dose sampling.

19.2.4 Analyses

A requirement of TDM is that drug concentrations can be measured and the results returned quickly to the clinician. In some instances this means while the patient is visiting the clinic. To achieve this rapid turnaround, immunoassays, point-of-care testing (POCT) kits, which are often based on immunoassays, and chromatographic techniques such as high performance liquid chromatography (HPLC), sometimes coupled to mass-spectrometry, with short and/or narrow bore columns are employed.

Manufacture of a number of non-isotopic immunoassays compatible with high-throughput clinical chemistry analysers has meant that certain TDM assays are widely available. It is important that the limitations and cross-reactivities of such assays are understood. Particular difficulties have arisen with digoxin immunoassays because of cross-reactivity with cortisol, spironolactone and substance(s) referred to as 'digoxin-like immunoreactive substances' (DLIS) which were first observed in patients with a variety of volume-expanded conditions: namely, diabetes, uraemia, essential hypertension, liver disease, and pre-eclampsia. DLIS cross-react with many antidigoxin antibodies and may falsely elevate plasma digoxin concentrations.

In fact, POCT kits are not often available for therapeutic drugs although there is one based on colorimetric analysis of lithium available in the United States. A kit for serum theophylline was introduced but does not appear to have been adopted widely. Most POCT kits have been developed and marketed for detecting drugs of abuse.

Chromatographic methods require extensive resources in terms of hardware and operator expertise. However, chromatographic assays are important in the case of amiodarone (where it has proved impossible to produce an antibody that does not cross-react significantly with thyroxine and tri-iodothyronine), antiviral drugs, immunosuppressants, many psychoactive compounds, and generally where active metabolites should be measured as well as the parent compound. Examples include carbamazepine/carbamazepine-10,11-epoxide, procainamide/*N*-acetylprocainamide, and amitriptyline/nortriptyline.

Whatever technique is used when providing a TDM service, adherence to the principles of quality management (proper method implementation and validation, and adherence to internal quality control and external quality assessment procedures) is essential as treatment decisions may be based on the results.

19.2.5 Reference ranges

A key requirement of TDM is that the clinical effects of a drug are in some way related to its plasma concentration even if the relationship between the plasma concentration and the concentration of drug at its site of action is complex. Drugs with a narrow therapeutic window will have a small range of concentrations below which the desired effect is suboptimal, and above which adverse effects may become so serious as to indicate dose reduction. Extreme examples are the immunosuppressants used to prevent organ rejection after transplantation. Too little drug may result in loss of the new organ, but too much drug is likely to result in infection, which is often life-threatening. In the longer term use of these drugs may result in development of malignancy.

Because patients vary so much in how they respond to drugs, the term *therapeutic range* is usually applied to an individual, that is, it is the range of concentrations applicable to *that* patient. To reflect this, the term *reference range* is recommended when helping interpret TDM data, although the expressions 'therapeutic range' or 'target range' may also be encountered. It is often useful to take a sample for analysis when treatment is deemed to be satisfactory, thereby establishing a target concentration for that patient – leading to individualized therapy.

Furthermore, it is important patient treatment is based on sound clinical judgement and not solely on the basis of a laboratory TDM result; to quote Reynolds and Aronson (1993): 'Treat the patient, not the plasma drug concentration'. However, for some drugs such as lithium, it is usual to adjust the dosage to achieve concentrations in the the target range.

19.3 Specific examples

19.3.1 Antiasthmatic drugs

There is usually no reason to monitor those bronchodilators, such as salbutamol and ipratropium, that are commonly taken by inhalation, as the clinical effect is easily assessed and the drugs are relatively non-toxic, even if taken in overdose. Also, they may not reach plasma in detectable quantities. In contrast, theophylline is administered orally, and this drug is monitored to minimize the risk of adverse effects that occur at relatively high plasma concentrations. Theophylline, a metabolite of caffeine, is metabolized to 3-methylxanthine, which is itself further metabolized by xanthine oxidase (Figure 19.1). Theophylline decays according to a two-compartment model with first-order kinetics although the two phases are rarely seen with oral dosing. The half-life of the terminal phase varies from 3–13 hours, providing for much variation in plasma

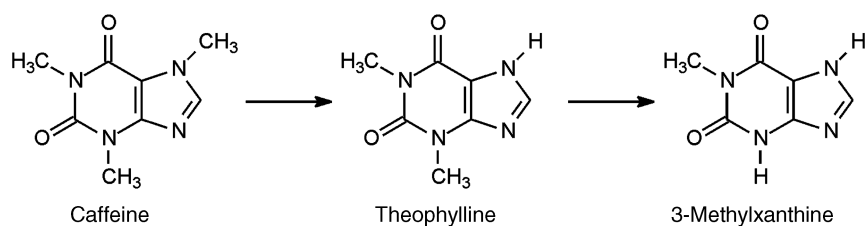

Figure 19.1 Theophylline is a metabolite of caffeine.

concentrations. When the half-life is short, such as in patients in whom the half-life is 5 hours, the fall from peak to trough within each dosage interval can be more than 50% of the peak. Because the therapeutic range is limited to peaks of approximately twice the troughs, this can result in fluctuation involving peaks and troughs outside the therapeutic range, unless dosing is inconveniently frequent. This problem is solved by the judicious use of controlled-release formulations, which reduces the extent of the fluctuation. In children, the C^{ss} concentrations are relatively close to the *K*m, and thus in children theophylline commonly exhibits dose-dependent kinetics, so that relatively small increases in dose result in relatively large increases in theophylline concentrations in plasma.

A variety of effects correlate with theophylline plasma concentrations, including improvement in forced expiratory volume, reduced frequency of asthma attacks, and increases in forearm blood flow. The adult reference range is 8–20 $mg\,L^{-1}$. Adverse effects (anorexia, nausea, vomiting, nervousness and anxiety) become increasingly evident towards 20 $mg\,L^{-1}$. Above 20 $mg\,L^{-1}$ sinus tachycardia and arrhythmias become a problem, and above 40 $mg\,L^{-1}$, local or generalized seizures and cardiorespiratory arrest are possible. Because prevention of unwanted effects is the most important reason for TDM with theophylline, it is usual to monitor peak concentrations at approximately 2–3 hours post-dosage. There is usually no need for monitoring of theophylline metabolites, but theophylline can be methylated to caffeine by neonates, although not by young children or adults. When theophylline and caffeine are used to treat neonatal apnoea the reference ranges are 6–12 and 10–30 $mg\,L^{-1}$, respectively.

19.3.2 Anticonvulsant drugs

There are clear indications for monitoring anticonvulsant drugs. They are used prophylactically to prevent seizures, which occur at irregular intervals so it is difficult to assess the efficacy of the treatment, in that prevention of incidents, rather than a graded effect, is sought. In general anticonvulsant drugs have low therapeutic indices and the toxicity is often difficult to access. The drugs are metabolized via the cytochrome P-450 pathways and phase 2 glucuronidation, so there are large interpatient differences in the degree of metabolism. The enzymes are prone to induction or inhibition leading to potential drug-drug interactions. Several of the class (especially phenytoin) exhibit non-linear kinetics (Section 4.3.), are highly protein bound and many have pharmacologically active metabolites, including primidone → phenobarbital, carbamazepine → 10,11-carbamazepine epoxide and clobazam → *N*-desmethylclobazam. Non-linear kinetics result in the time to the pharmacokinetic steady-state being variable (i.e. relatively long at relatively high doses), and, clinically, a pharmacokinetic steady-state with minimal or zero fluctuation between peaks and troughs is sought. Epilepsy is usually diagnosed at an early age, but is a chronic condition that may require lifetime treatment. Thus it is almost certain that treatment will have to be changed as the patient ages and over 30% of patients are treated concomitantly with two or more anticonvulsant drugs.

The earliest studies related to monitoring of anticonvulsants concerned phenytoin and were published in the 1960s when unsuccessful control of seizures was linked to inadequate plasma concentrations in long-term therapy. At the same time, a considerable factor affecting phenytoin concentrations was shown to be concomitant use of other drugs. Furthermore, decreasing paroxysmal activity in the EEG was shown to correlate with increasing drug concentrations, thereby establishing a dose–response relationship. In the 1970s, studies showed concentration–effect relationships for several of the available anticonvulsants including phenobarbital, primidone and ethosuximide.

Since 1990, the number of antiepileptic drugs available has more than doubled and it may be prudent to add these to the list of drugs that should be monitored. Gabapentin, levetiracetam, pregabalin, topiramate, and vigabatrin are eliminated largely or completely unchanged in urine. Hence, plasma concentrations may be affected by alterations in renal function. Gabapentin shows dose-dependent bioavailability. Concomitant use of enzyme-inducing drugs can affect topiramate concentrations markedly. For the newer drugs that

are largely metabolized prior to excretion (felbamate, lamotrigine, oxcarbazepine, tiagabine, and zonisamide), interpatient variability in pharmacokinetics is just as important in dose adjustment as for many older anticonvulsants.

In newly diagnosed patients there is no clear evidence to support the use of TDM with the aim of reaching predefined target ranges in dose optimization with anticonvulsant monotherapy. However, reference ranges have been proposed (Table 19.1) that might guide dosing when necessary. The dose should not be adjusted if the patient is seizure-free but the serum concentration is below the lower limit. In fact it has been suggested that phenytoin, phenobarbital, carbamazepine and valproic acid should only have upper values.

Table 19.1 Bioavailability, protein binding and reference ranges for selected anticonvulsant drugs (adapted from Patsalos *et al*., 2008)

Drug	Oral availability (%)	Serum protein binding (%)	Time to steady-state (days)	Reference range ($mg\,L^{-1}$)
Carbamazepine	≤85	75	2–4[a]	4–12
−10,11-expoxide				0.5–2.5
Clobazam	≥95	85	7–10	0.03–0.3
desmethyl–				0.3–3
Clonazepam	≥95	85	3–10	0.02–0.07
Ethosuximide	≥90	0	7–10	40–100
Felbamate	>90	25	3–4	30–60
Gabapentin	<60[b]	0	1–2	2–20
Lambotrigine	≥95	55	3–6	2.4–15
Levetiracetam	≥95	0	1–2	12–46
Oxcarbazepine[c]	90	40	2–3	3–35
Phenobarbital	≥95	55	12–24	10–40
Phenytoin	≥80	90	5–17	10–20
Primidone	≥90	10	2–4	5–10[d]
Tiagabine	≥90	96	1–2	0.02–0.2
Topiramate	≥80	15	4–5	5–20
Valproic acid	≥90	90[e]	2–4	50–100
Vigabatrin	≥60	0	1–2	0.8–36
Zonisamide	≥65	50	9–12	10–40

[a]Initially; steady-state takes up to 5 weeks because of autoinduction. [b]Bioavailability decreases with increasing doses. [c]Prodrug; all values refer to active metabolite. [d]Phenobarbital should be monitored as well. [e]Binding decreases with increasing concentrations.

Some authorities promote the idea of measuring unbound concentrations of anticonvulsants in TDM protocols, but this is technologically more complex and is relatively expensive. Different ranges then apply. The process of dose-adjustment with phenytoin is considered in a later section.

19.3.3 Antidepressants

Successful use of antidepressant drugs is complicated because:

- Some 20–40% of patients respond to placebo within 3–4 weeks of treatment.
- Some patients remain unresponsive irrespective of dose.
- The rate of metabolism can vary by 30–40-fold between subjects.
- Compliance is a problem.

- Patients may become tolerant to some of the unwanted effects.
- The mechanism of action is not understood and clinical effects are not usually seen until two or more weeks after initiation of treatment.

Also, several of the drugs are metabolites of other antidepressants. The first example of this was the prescribing of imipramine, which was quickly followed by the introduction of desipramine, but this mode of new product discovery has continued into the 21st century with venlafaxine and desvenlafaxine. In such cases TDM must often involve pairs of compounds of different potencies and with different pharmacokinetic properties. There have been attempts to relate the antidepressant response to objective clinical pharmacological tests, such as tyramine-induced hypertension and disturbance of accommodation, but these have not found widespread application in patient care. It is sometimes thought with these drugs that there is an important dose-related response in each subject that does not translate into a population-wide phenomenon. The small therapeutic windows exhibited by the tricyclic antidepressants (imipramine, nortriptyline, etc.) make these drugs candidates for therapeutic monitoring, however establishing agreed reference ranges has proved difficult. Several studies in the 1970s produced conflicting results but did usefully show that the concentration–response relationships could be an inverted U-shape (Curry, 1980). A typical example is shown in Table 19.2, albeit with relatively small numbers of patients.

Table 19.2 Relationship between nortriptyline plasma concentrations and response – global rating as 'amelioration score (Asberg *et al*., 1971)

Plasma concentration ($\mu g\,L^{-1}$)	Number of patients	Amelioration score	
		Mean	SEM
≤ 49	5	0.4	1.2
50–79	10	6.2	0.8
80–109	4	6.1	1.4
110–139	5	5.0	2.0
≥ 140	5	1.2	1.9

Even today there is no consensus over the role of TDM in psychiatric medicine. In practice, TDM of TCAs and also of selective serotonin reuptake inhibitors (SSRIs) and other newer antidepressants such as venlafaxine is mainly concerned with assessing whether treatment failure is due to poor adherence, ultra-rapid metabolism, or drug interactions leading to induction of metabolizing enzymes. Compliance is a problem, a study showing that during a 3-month treatment with SSRIs, 72.5% of the patients missed at least 1 dosing day, and 29% of the patients had missed 2 or more days, consecutively. Many of the class, particularly the SSRIs are metabolized by CYP2D6 and so the levels are affected by genetic differences (Section 10.5.1) and prone to drug–drug interactions. It as been suggested that phenotyping of patients should also be conducted.

Although reference ranges have been suggested (Table 19.3) a survey of 33 UK laboratories showed a high degree of variability (Wilson 2003). The range of values was greater than 100-fold for some compounds, particularly for the minimum effective concentrations. For example the lower limit for paroxetine ranged from 1 to 170 $nmol\,L^{-1}$ (mean 70 $nmol\,L^{-1}$).

Table 19.3 Reference ranges for plasma concentrations of selected antidepressants and active metabolites in adults

Drug	Reference range ($mg\,L^{-1}$)
Amitriptyline + nortriptyline	0.08–0.25
Citalopram	0.05–0.5
Clomipramine + norclomipramine	<1.0
Desipramine	0.08–0.16
Escitalopram	0.025–0.25
Fluoxetine	0.04–0.45
norfluoxetine	0.04–0.45
Fluvoxamine	0.16–0.22
Imipramine + desipramine	0.15–0.25
Nortriptyline	0.05–0.15
Paroxetine	0.01–0.05
Sertraline	0.03–0.19
Trimipramine + nortrimipramine	<0.50
Venlafaxine	0.05–0.5
O-desmethylvenlafaxine	0.05–0.5

19.3.4 Antimicrobial agents

The reasons for monitoring antimicrobial agents are much the same as for any other class of drugs. They are to check (i) that the concentrations are sufficient for efficacy but below those associated with toxicity, (ii) the bioavailability following a switch from i.v. to oral dosing, (iii) for compliance, particularly in patients receiving drugs for tuberculosis/multidrug resistant TB.

Antimicrobial drugs can be divided into those whose effect is primarily related to the concentration of drug (i.e. the higher the concentration the greater the kill), and those for which the time of exposure is important (i.e. increased time of exposure increases the kill). Consequently, three parameters may be assessed: (i) the time that the concentration is a above the minimum inhibitory concentration (MIC, which is measured *in vitro* for the pathogen under consideration), (ii) the ratio of the peak concentration to the MIC, and (iii) the area under the 0–24 hour plasma concentration to MIC ratio (Figure 19.2).

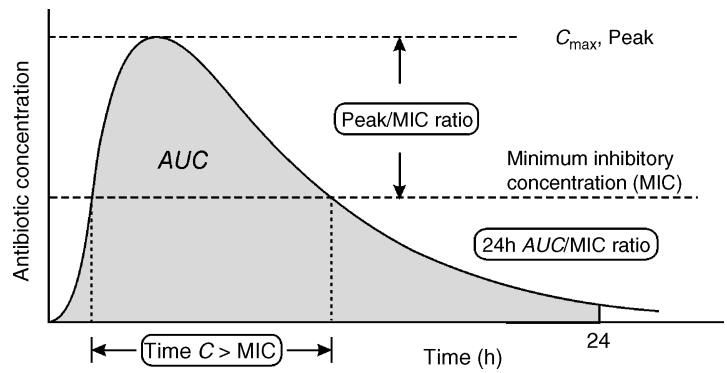

Figure 19.2 Schematic representation of parameters that might be assessed for therapeutic monitoring of antimicrobial drugs.

The process of setting up a dosing regimen for gentamicin is considered later. Gentamicin can be described as having the remarkable property of an inverse safety margin – peaks need to be above 5 mg L^{-1} in order to achieve a successful bacterial kill, but troughs need to be below 2 mg L^{-1} in order to prevent toxicity. Gentamicin and other aminoglycosides fall into the concentration-dependent category and the aim is to achieve the maximum tolerable concentrations – the appropriate parameters are C_{max}/MIC or *AUC*/MIC. For the β-lactam antibiotics the duration of exposure is important and the length of time above the MIC is the appropriate parameter. In the case of vancomycin, the *AUC*/MIC ratio is used as it is the amount of drug to which the pathogens are exposed that is important.

Monitoring of some antimicrobials is carried out in most, if not all, in-patients. These include the antibacterials, gentamicin, vancomycin, streptomycin and antifungals, itraconazole and flucytosine. The aim with gentamicin is a C_{max}/MIC ratio of 8–10 with trough concentrations less than 1–2 mg L^{-1}. Vancomycin trough concentrations should be below 10–12 mg L^{-1} before the next dose is given. Ototoxicity may occur at concentrations >80 mg L^{-1}. Optimum concentrations of flucytosine have not been established but myelosuppression may occur above 100 mg L^{-1}.

19.3.5 Cardioactive drugs

19.3.5.1 Digoxin

Digoxin plasma concentrations in plasma are very low (0.1–5 μg L^{-1}) and are usually measured by immunoassay (IA). The drug is excreted to a considerable extent as unchanged drug in urine, and its plasma concentrations are therefore influenced by renal function. Also, there are formal protocols for dosage adjustment based on objective measurements of renal function. Other factors affecting digoxin concentrations are bioavailability, age, weight and plasma albumin. Pharmacodynamic influences include ion balance (potassium, magnesium, calcium), acidosis and alkalosis, and oxygen tension. Hypokalaemia and hypomagnesaemia may increase the myocardial sensitivity to digoxin.

At one time, clinical practice involved increasing the digoxin dose until unwanted effects were seen, and then cutting back to a dose just below the threshold for these unwanted effects. This process was termed 'digitalization'. It is now realized that the condition sometimes being treated in many patients (arrhythmias) and the most prominent unwanted effects have so much in common that it can be difficult to determine whether a patient receiving digoxin and experiencing arrhythmia is underdosed or overdosed. Redfors (1972) demonstrated a correlation between slowing of ventricular rate and digoxin concentrations in patients with atrial fibrillation. This was a within patient study. In patients with congestive heart failure who have been prescribed cardiac glycosides for their positive inotropic effect, there is no easy way of accessing efficacy and the manifestation of toxicity (anorexia, nausea, vomiting and cardiac arrhythmia) are also signs and symptoms of the disease. Thus, plasma level monitoring may aid dosage adjustment in such circumstances. Having said that, the therapeutic index is very low (0.8–2 μg L^{-1}) and there is considerable overlap between toxic and non-toxic concentrations as can be seen from Figure 19.3, although children can tolerate relatively high levels.

Digoxin has two-compartment distribution properties, and the drug penetrates slowly to its receptors, so monitoring is based on trough concentrations, with plasma samples collected some 8–24 hours after the time of the dose that precedes them. Digitoxin concentrations are also sometimes monitored when that drug is prescribed.

19.3.5.2 Antidysrythmic drugs

Drugs under this broad heading include the membrane stabilizing drugs (sodium channel blockers: lidocaine, phenytoin, quinidine and procainamide), β-adrenoceptor blockers and calcium channel antagonists, such as

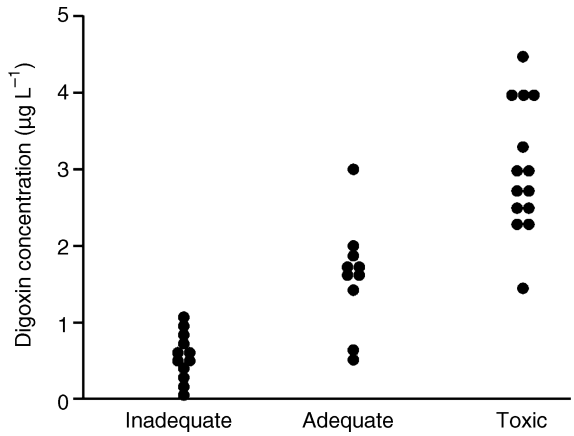

Figure 19.3 Plasma digoxin concentrations in patients judged to be inadequately digitalized, adequately digitalized and showing symptoms of toxicity. (Redrawn after Oliver *et al.*, 1971.)

verapamil. Reference ranges for some of this class of drugs are presented in Table 19.4. A relationship between the degree of antagonism of isoprenaline-induced tachycardia by propranolol and concentrations of the drug in plasma has been shown.

Table 19.4 Reference ranges for selected antidisrhythmic drugs (Flanagan *et al.*, 2008)

Drug [metabolite]	Reference range in an adult (mg L^{-1} plasma)
Amiodarone	0.5–2
[Noramiodarone]	[0.5–2]
Atenolol	0.2–0.6
Disopyramide	2.0–5.0
[Nordisopyramide]	[<5.0]
Flecainide	0.2–0.7
Lidocaine	1.5–5.0
Metoprolol	0.2-0.8
Procainamide [+ acecainide]	10–30 (procainamide only, 4–8)
Propranolol	0.01–0.1
Quinidine	2.5–5.0
Sotalol	0.8–2.0 (β-blockade), 2.5–4.0 (antiarrhythmic)
Verapamil	0.1–0.2
[Norverapamil]	[0.1–0.2]

Metabolites that are usually measured are shown thus [ ].

TDM can sometimes be useful in the case of amiodarone to monitor adherence and toxicity, and to monitor adherence to sotalol and to other β-adrenoceptor blockers such as atenolol and propranolol. Use of the calcium channel blockers verapamil and diltiazem is normally assessed by monitoring haemodynamic effects. Diltiazem and *N*-desmethyldiltiazem, desacetyldiltiazem and *N*-desmethyldesacetyldiltiazem are unstable in plasma and all may be pharmacologically active. The rate of metabolism of procainamide to *N*-acetylprocainamide (acecainide) is influenced by acetylator status (Section 10.3)

19.3.6 Immunosuppressives

Monitoring of immunosuppressants, used to prevent organ rejection after transplantation, is extremely important to ensure their safe and effective use. Too little drug may result in loss of the new organ, but too much drug is likely to result in infection, which is often life-threatening. Indeed, monitoring of sirolimus is a requirement of drug licensing within the European Union.

Ciclosporin, mycophenolic acid (the active metabolite of mycophenolate mofetil), sirolimus, and tacrolimus are monitored (Table 19.5). However, some patients experience acute rejection episodes or postoperative complications even when the blood concentrations are within the reference range. *AUC* values may give more useful information than measurements at a single time point particularly for mycophenolic acid. Clearly, serial blood sampling is likely to be impractical in an out-patient setting, hence the suggestion that samples collected 2 hours post-dose (so called 'peak' concentrations) are a suitable surrogate for *AUC* (Section 19.1.3). This has not been adopted universally and, in any event, peak sampling is difficult to achieve in practice. Interpretation of either 'trough' or 'peak' results is complicated because:

- There may be considerable differences between the results obtained with immunoassays when compared with chromatographic methods.
- Immunosuppressants are often used in combination to reduce the risk of toxicity from individual compounds hence the concentrations attained during optimal treatment are lower then when the drugs are used alone.
- The amount of immunosuppression required for maintenance treatment varies widely depending on the engrafted organ.

Table 19.5 gives reference ranges that are applicable to therapy with single immunosuppressants used after renal transplantation.

Table 19.5 Some immunosuppressive drug TDM assays (Flanagan *et al*., 2008)

Drug	Reference range in adults ($mg\,L^{-1}$)[a]
Ciclosporin	0.04–0.25 (trough, whole blood)[b]
Mycophenolic acid	2.5–4.0 (trough, plasma)
Sirolimus	0.003–0.015 (trough, whole blood)
Tacrolimus	0.001–0.012 (trough, whole blood)

[a]Single immunosuppressant, renal transplant patients.
[b]IA may be unreliable in some patient groups (e.g. neonates, renal failure, hepatic failure).

19.3.7 Lithium

Lithium was the first drug to be monitored with a view to better clinical control of symptoms, and it remains the one drug for which knowledge of pharmacokinetics is almost essential if optimum therapy is to be achieved, in regard to both efficacy and safety. Lithium is interesting in that:

- It has a narrow margin of safety.
- It is an inorganic ion, and so has no complicating metabolites.
- It has predictable pharmacokinetic properties which allow definition of an individual dosage regimen: each patient may be different but the changes within a subject are predictable.
- It is nephrotoxic, which increases the risk of accumulation.

Serum lithium concentrations are very variable between individuals because of variations in the rate and extent of absorption, renal clearance and apparent volume of distribution. The elimination half-life ranges from 7–41 hours. Because of the fluctuations in concentrations within a dosage period, and diurnal variation, it has been recommended that samples be taken 12 hours after the last dose and at the same time of day, preferably in the morning. The concentrations are referred to as 'standardized 12 hour' concentrations and are thus the trough concentrations in a twice daily dosing regimen.

With lithium the reference range is a true target range. Recommended concentrations are 0.8–1.2 mmol L^{-1} for the treatment of acute mania, whilst 0.4–0.8 mmol L^{-1} is usually suitable for the prophylaxis of unipolar or bipolar illness. Toxicity is usually associated with serum concentrations >1.4 mmol L^{-1} and a vicious circle of toxicity involving renal damage and subsequent drug accumulation can be set in motion in the range 1.5–2 mmol L^{-1}. Concentrations over 2 mmol L^{-1} are associated with a high incidence of toxicity and death can occur above 3 mmol L^{-1}. The problem of fluctuating serum concentrations, which can lead to inattention, lethargy, ataxia and tremor (thought to be associated with peak concentrations) can be reduced by the use of sustained-release preparations.

Situations which can lead to increased lithium concentrations include reduced glomerular filtration, sodium depletion, diuretics (principally thiazides) and non-steroidal anti-inflammatory drugs. Thus, fever and diarrhoea lead to toxicity. As with theophylline, the half-life in an individual can be so short that the fluctuation at the pharmacokinetic steady-state is at risk of inducing concentrations above and below the desired range, and controlled-release medication has a role to play in reducing this level of fluctuation.

19.3.8 Neuroleptics

There is little need for routine monitoring of the established ('typical') antipsychotics such as chlorpromazine and haloperidol, as these are not considered as toxic as the tricyclic antidepressants. However, it can be difficult to distinguish the signs of overdose from some of the signs of the disease being treated with some of these drugs, and studies have shown inverted U-shape plasma concentration–response relationships with high concentrations being associated with poor or no response. Such an observation can also indicate inappropriate choice of drug or misdiagnosis. Indications for monitoring include patients who do not respond to high doses to confirm correspondingly high concentrations and those suspected of non-compliance. Testing for compliance requires establishment of pharmacokinetic steady-state plasma concentrations during successful therapy for comparison. Large fluctuations in concentrations on repeat testing may indicate that there are periods of non-compliance. Determining 'effective' plasma concentrations in patients undergoing successful therapy may be helpful in providing a 'target value' for that patient that can be used for subsequent treatment on readmission, when there may be a drug interaction or when the formulation is changed.

The ability to monitor anti-schizophrenia medication using plasma concentration measurements became possible at a time when large numbers of psychiatric patients were kept in hospitals for as much as two years for the treatment of acute episodes and sometimes for the rest of their lives if treatment was unsuccessful. Also, many patients on phenothiazine drugs at this time suffered from a debilitating condition termed 'tardive dyskinesia', which resembled some aspects of Parkinson's disease, with both inappropriate spontaneous movement disorders and also extreme difficulty in co-ordinating normal movement. This dyskinesia was termed 'tardive' because it developed slowly with long-term treatment. It was sometimes irreversible. It occurred because there had been a treatment concept not unlike that of digitalization with digoxin, leading to dose increases until unwanted effects were observed, then reduction of dosage to just below the threshold for what was presumed to be the desired effect. Unfortunately, the dose reduction stage of this process did not always work, and the patients became victims of what was effectively planned overdosing. The insight into such problems that was possible as the result of pharmacokinetic studies contributed, in part, to a complete change in prescribing philosophy, away from 'as much as could be tolerated', to 'treatment with the lowest

dose consistent with a useful effect', and the acute phase of schizophrenia was dramatically shortened, and the risk of a need for long-term treatment was greatly reduced. At the same time, social pressures led to the closing of long-term psychiatric facilities, and this was made possible, by the new emphasis on drug exposure governed by pharmacokinetic principles, including the use of sustained-release preparations such as fluphenazine decanoate.

Monitoring newer, second generation or 'atypical' neuroleptics, notably clozapine and to an extent olanzapine, can help by assessing compliance, guiding dose adjustment, and guarding against toxicity. With clozapine dose assessment is complicated because: (i) there is a 50-fold inter-patient variation in the rate of clozapine metabolism, (ii) alteration in smoking habit can have a dramatic effect on clozapine dose requirement (on average $\pm 50\%$), and (iii) the clinical features of clozapine overdosage can mimic those of the underlying disease. A range of 350–500 $\mu g\,L^{-1}$ is considered suitable for clozapine, although the upper limit is ill-defined. Plasma concentrations of the desmethyl metabolite are approximately 70% of those of the parent drug during normal therapy so monitoring norclozapine can help in accessing compliance or correct timing of sample collection. With olanzapine, a 12-hour post-dose plasma concentration of 20 $\mu g\,L^{-1}$ has been suggested.

19.3.9 Thyroxine

The normal thyroid gland produces both tri-iodothyronine (T3) and tetra-iodothyronine (T4), which control a wide variety of body functions connected with maintenance of normal metabolic activity. Increases or decreases in these hormones cause changes in blood concentrations of thyroid-stimulating hormone (TSH), which is secreted by the pituitary gland to, in turn, control the thyroid gland. Thus increases in T3 and/or T4 in the blood lead to decreases in TSH. Therapy of thyroid disorders often involves administration of thyroxine, which is T4. Thyroxine dosing is mostly monitored by means of TSH measurement, rather than by direct T3 and/or T4 measurement, so TSH achieves the status of monitoring of therapy using an endogenous biochemical (biomarker). Quite small (10%) changes in thyroxine dose can lead to dramatic (doubling or halving) changes in TSH.

19.4 Dose adjustment

For the most part, dosing adjustment in response to concentration measurements is straightforward, linear pharmacokinetic properties and the fact that most therapy occurs within a linear range of effect in relation to concentration, dictate that linear dose adjustments can be made. For example, if the desired concentration is 15 $mg\,L^{-1}$, and the measured concentration is 10 $mg\,L^{-1}$, then the dose can be increased by 50%. However, two examples, gentamicin and phenytoin deserve special attention in this context.

19.4.1 Gentamicin

In devising a gentamicin dosing regimen optimized for a particular patient, an early dose is first used for calibration purposes. This dose is infused for 30–60 minutes. This is followed by a 30–60 minute interval during which equilibration among the compartments takes place, after which a first blood sample for drug analysis is collected ('peak'). A second sample is collected just before the next dose is administered ('trough'), and a half-life is calculated from these two-points. Simple pharmacokinetic calculations are used to adjust the peak to be between 5 and 12 $mg\,L^{-1}$ (depending on the characteristics of the infection involved), and the trough to $<2\,mg\,L^{-1}$. The peak is adjusted by changing the dose, and the trough is adjusted by changing the dosing interval. Finally, the dose and interval are fine-tuned to meet both the

medical need and the need for a convenient dosing interval, which needs to be a simple fraction of 24 hours. Figure 19.4 shows a typical pattern of development of an optimal gentamicin dosing interval.

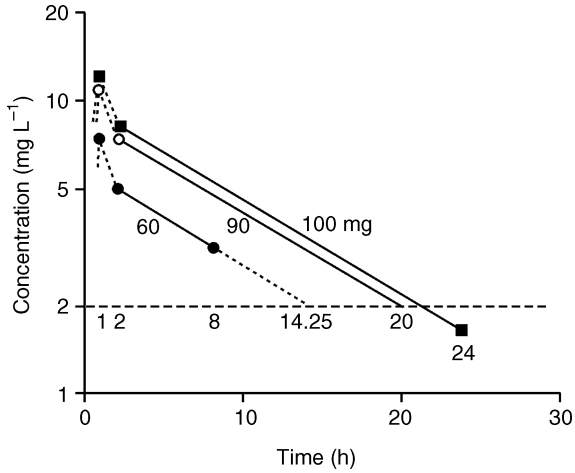

Figure 19.4 Development of a gentamicin dosage regimen. The graph shows the concentration in plasma *versus* time data following a test dose of 60 mg, and assays at 2 and 8 h after starting the 1 hour infusion. A 90 mg dose was proposed, predicting a peak concentration of 7.5 and a trough of 2.0 mg L^{-1} at approximately 20 h. A 100 mg dose gives an acceptable peak and a trough <2.0 mg L^{-1} at a convenient dosing interval of 24 h.

19.4.2 Phenytoin

Figure 4.13(a) shows how phenytoin concentrations vary with dose. Equation 4.44 shows how respect for the Michaelis–Menten kinetics that apply to this drug can be used to plot a straight line relationship between daily dose, and daily dose divided by C^{ss}, and this is illustrated by Figure 19.5(a). This

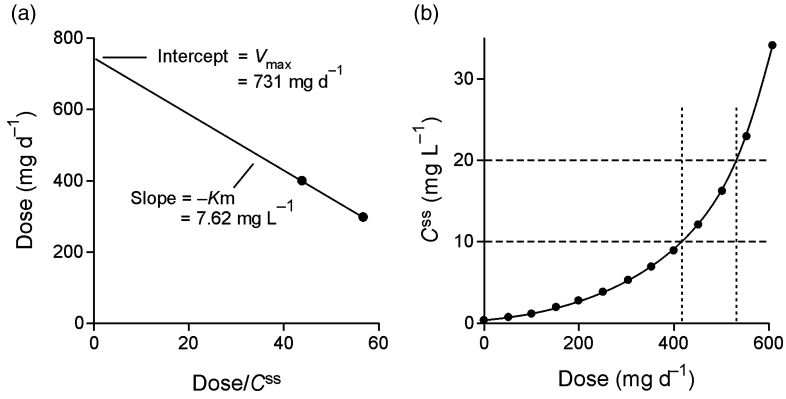

Figure 19.5 (a) Simulated experiment for determination of V_{max} and *K*m in a patient treated with two doses of phenytoin (300 and 400 mg per day), giving C^{ss} values of 5.3 and 9.2 mg L^{-1}, respectively. (b) Calculated steady-state concentrations as function of daily dose using the V_{max} and *K*m values derived in (a).

relationship gives a slope of $-K$m and an intercept on the y-axis (daily dose) of V_{max}. Note that this is V_{max} with units very different from those conventionally used in enzymology or for maximum rate of change of concentrations in blood. Data are first collected by dosing to pharmacokinetic steady-state with one dosing regimen, measuring C^{ss}, then dosing to a new steady-state with another regimen, and measuring C^{ss} again. Up to 6 weeks may be needed to reach steady-state in each case. Knowing V_{max} and Km for the patient, the C^{ss} predicted to occur with any regimen from 0 to V_{max} mg phenytoin per day can be calculated. A regimen giving C^{ss} between 10 and 20 mg L^{-1} can then be devised. Figure 19.5(b) shows a graph of C^{ss} against daily dose for the patient of Figure 19.5(a) in whom V_{max} was 731 mg day^{-1} and Km was 7.6 mg L^{-1}.

This approach does not meet all clinical needs, mainly because of the long times needed to reach steady-state. In fact, the time to reach steady-state can only be calculated, and then only as a time to reach a specific fraction of C^{ss}, if V_{max} and Km are known in advance – clearly a practical impossibility. Additionally, this approach fails if the values of Km and V_{max} change during the time over which the investigation takes place, for example because of enzyme induction. So, clinicians will tend to apply a rule of thumb in choosing the second dosing regimen, along the following lines, in the hope of choosing the optimum dose at the earliest possible time:

- If the measured initial concentration is <7 mg L^{-1}, then increase the dose by 100 mg day^{-1} or more.
- If the measured concentration is in the range 7–12 mg L^{-1}, then increase the dose by 50–100 mg day^{-1} if there is an obvious clinical need.
- If the measured concentration is >12 mg L^{-1} then increase the dose by 30–50 mg day^{-1}, again if there is an obvious clinical need.

These adjustments obviously precede the second sample, and measured serum concentrations will validate them or lead to further adjustments.

Several other approaches to this computation have been devised, notably by Graves and Cloyd, by Mullen and by Vozeh and Sheiner (see Bauer, 2001). All can be computerized, and all give valuable and complementary outcomes.

19.5 Summary

It should be remembered that not all drugs need monitoring. There is little point in investing in TDM if the results will not answer a clinical question. Ideally, a relationship between plasma concentrations and therapeutic outcome will have been established but even if this is not clear, ensuring compliance and individualizing patient treatment may be a benefit. High degrees of analytical accuracy and precision are required if the results are to be meaningful and, of course, the results have to be available when required. Having said that, previously we described the evolution of the discipline of pharmacokinetics from an initial phase (1900–1950) dominated by the scientific curiosity of the likes of Teorell, Dost and Widmark, a phase related to optimum design of dosage forms, dominated by such people as Nelson, Levy, Riegelman, Garrett, Gibaldi and Perrier, and many others, a phase of application in clinical pharmacology inspired by the writings of Brodie and the many scientists in Europe and North America, as well as other places, who have taken an interest in the field, and a recent phase of application in new drug design in the pharmaceutical industry. The use of pharmacokinetics in optimizing therapy with gentamicin and phenytoin would seem to be a high point in the validation of the subject in both pure and applied senses, although it is to be hoped that future drugs will not have the properties that have made this elegant work necessary.

References and further reading

Aronson JK, Hardman M, Reynolds DJ. ABC of monitoring drug therapy. Phenytoin. *BMJ* 1992; 305: 1215–8.

Asberg M, Cronholm B, Sjoqvist F, Tuck D. Relationship between plasma level and therapeutic effect of nortriptyline. *Br Med J* 1971; 3: 331–4.

Bauer LA. *Applied Clinical Pharmacokinetics* New York, McGraw Hill, 2001.

Baumann P, Hiemke C, Ulrich S, Gaertner I, Rao ML, Eckermann G, *et al*. Therapeutic monitoring of psychotropic drugs: an outline of the AGNP-TDM expert group consensus guideline. *Ther Drug Monit* 2004; 26: 167–70.

Curry SH. *Drug Disposition and Pharmacokinetics*, 3rd edn. Oxford: Blackwell Scientific, 1980.

Edwards LD, Fletcher AJ, Fox AW, Stonier PD. *Principles and Practice of Pharmaceutical Medicine*, 2nd edn. Chichester: John Wiley & Sons, 2007.

Flanagan RJ, Brown NW, Whelpton R. Therapeutic drug monitoring (TDM). *CPD Clin Biochem* 2008; 9: 3–21.

Jorga A, Holt DW, Johnston A. Therapeutic drug monitoring of cyclosporine. *Transplant Proc* 2004; 36(2 Suppl): 396S–403S.

Oliver GC, Parker BM, Parker CW. Radioimmunoassay for digoxin. Technical and clinical application. *Am J Med* 1971; 51: 186–92.

Olsen CK, Brennum LT, Kreilgaard M. Using pharmacokinetic-pharmacodynamic modelling as a tool for prediction of therapeutic effective plasma levels of antipsychotics. *Eur J Pharmacol* 2008; 584: 318–27.

Patsalos PN, Berry DJ, Bourgeois BF, Cloyd JC, Glauser TA, Johannessen SI, Leppik IE, Tomson T, Perucca E. Antiepileptic drugs – best practice guidelines for therapeutic drug monitoring: a position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. *Epilepsia* 2008; 49: 1239–76.

Peck CC, Conner DP, Murphy MG. *Bedside Clinical Pharmacokinetics*. Washington: Applied Therapeutics Inc, 1989.

Redfors A. Plasma digoxin concentration – its relation to digoxin dosage and clinical effects in patients with atrial fibrillation. *Br Heart J* 1972; 34: 383–91.

Remington G, Shammi CM, Sethna R, Lawrence R. Antipsychotic dosing patterns for schizophrenia in three treatment settings. Psychiatr Serv 2001; 52: 96–8.

Reynolds DJ, Aronson JK. ABC of monitoring drug therapy. Making the most of plasma drug concentration measurements. *Bmj* 1993; 306: 48–51.

Van Putten T, Marder SR, Wirshing WC, Aravagiri M, Chabert N. Neuroleptic plasma levels. *Schizophr Bull* 1991; 17: 197–216.

White JR, Garrine MW. *Basic Clinical Pharmacokinetics Handbook*. Vancouver: Applied Therapeutics Inc., 1994.

Wilson JF. Survey of reference ranges and clinical measurements for psychoactive drugs in serum. *Ther Drug Monit* 2003; 25: 243–7.

Winter MF. *Basic Clinical Pharmacokinetics*, 2nd edn. Spokane: Applied Therapeutics Inc., 1987.

Yeung PK, Hubbard JW, Korchinski ED, Midha KK. Pharmacokinetics of chlorpromazine and key metabolites. *Eur J Clin Pharmacol* 1993; 45: 563–9.