Basics of TDM with example drugs

Pharmacokinetic differences in drug handling between patients produce wide variability in serum drug concentrations, but dosage adjustments are generally only required if there is serious organ damage such as severe renal impairment. Dosage requirements of individual patients can also vary significantly if a drug has a narrow therapeutic index. For these drugs, dose titration based on the response to the drug would be ideal, for example adjusting warfarin dose according to INR. However, therapeutic effect is not always easily measured and toxic effects may be non-specific. In these circumstances, assuming the relationship between the drug concentration and the response is known; measuring the concentration of the drug in the patient’s blood can prove useful information.¹

Therapeutic drug monitoring (TDM) refers to the individualisation of dosage by maintaining plasma or blood drug concentrations within a target range (therapeutic range, therapeutic window).² This range represents plasma concentrations generally associated with optimal effect and a low incidence of toxicity. It is a guide to therapy but must be used in conjunction with clinical response when assessing and adjusting dosage regimens. Dosage adjustment is not always required if the clinical response is appropriate but the plasma concentration is outside the accepted range ie treat the patient not the plasma level.³

TDM is costly in addition to being unpleasant and inconvenient for the patient. Therefore the reason for monitoring and the impact of additional information on clinical decisions must be carefully considered.³

TDM may be indicated in the following situations:³

- when initiating therapy or adjusting dose
- in the critically ill or patients with rapidly changing physiological status eg acute renal failure
- to confirm toxicity/lack of effect in a poorly controlled patient
- where a drug interaction is suspected
- as a measure of patient compliance

Drug concentrations are usually measured in whole blood or serum, although saliva, which gives a measure of the unbound drug concentration, may be useful when blood samples are difficult to collect. For example, measuring phenytoin concentrations in children.¹

The correct timing of sampling is important for accurate TDM. For most drugs the “target” concentrations are based on steady state samples taken at specific times after the dose. In most clinical situations, the attainment of steady state can be
assumed 3 to 5 half-lives after change in dose or initiation of therapy \(^4\) provided that the dose and clearance remain constant (unless loading doses are given). \(^3\) For most drugs, plasma samples should be taken just before the next dose (trough) as these levels are less likely to be influenced by absorption and distribution problems.\(^4\)

Assays measure drug that is both bound and unbound to plasma protein, but it is only the unbound drug that interacts with the receptor to produce a response. If binding is changed by disease states, displacement by another drug or non-linearity in protein binding, the interpretation of total plasma or blood drug concentrations must be modified to prevent inappropriate dose adjustments resulting in toxicity. \(^2\)

Another factor that should be considered when interpreting drug concentrations is whether the drug has active metabolites, as metabolites which may not be measured can contribute to the therapeutic response. \(^2\)

**Immunosuppressants**

Immunosuppression plays a vital role in preventing and treating allograft rejection in the transplant recipient and in the treatment of various autoimmune disorders. Many of the immunosuppressive drugs have a narrow therapeutic index in addition to exhibiting pharmacokinetic variability; both inter-patient and intra-patient. Subtherapeutic levels and wide fluctuations in drug levels are risk factors for graft rejection and decreased graft survival. TDM is essential in optimising the patient's immunosuppressive drug regimen to minimise the risk of rejection and dose-related adverse effects. \(^4\)

The therapeutic range for immunosuppression can vary according to transplant centre protocols and may be specific to the organ transplanted, time since transplant and indication for transplant. \(^4\)

**Cyclosporin**

The most common adverse effect associated with cyclosporin is renal dysfunction, which usually improves when the dose is decreased or drug is discontinued although can lead to irreversible renal failure. For this reason cyclosporin doses and target concentrations are often lowered in patients who show early signs of nephrotoxicity. Other dose-related adverse effects include neurotoxicity (headache, tremors, paresthesias, seizures) and hypertension. \(^4\)

Cyclosporin has limited and highly variable bioavailability, and although the most widely used method for monitoring cyclosporin therapy is to sample the trough concentration, this approach does not always correlate well with the patient’s exposure to drug. AUC is a much better predictor of response and the cyclosporin concentration at 2 hours after administration \((C_2)\) is the most accurate single sample marker for AUC. There is a 15 minute period before and
after the 2 hour time point, during which the C₂ sample can be taken to remain within an acceptable margin of error. ⁴ C₂ monitoring is no longer performed at CCDHB.

**Tacrolimus**
Tacrolimus also has a low bioavailability, ¹ and is associated with dose-related nephrotoxicity, neurotoxicity, post-transplant diabetes mellitus and hypertension. ⁴ Tacrolimus has a more consistent relationship between trough concentration and AUC, so therapy is usually based on trough measurements. ³

**Anti-convulsants**

**Valproate**
Sodium valproate is highly bound to plasma protein, and at therapeutic plasma concentrations, saturates plasma protein binding sites causing the amount of free drug to rise rapidly, out of proportion to any increase in dosage. ⁶ Correlation between the dose and plasma levels of valproate have been poor and levels are not a useful index of efficacy. Optimum dosage is mainly determined by seizure control and routine measurement of plasma levels is unnecessary. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side effects are suspected and to check adherence. ⁵

**Carbamazepine**
Carbamazepine has an active metabolite which makes interpretation of the plasma concentrations difficult. (1 Although correlations between dosage and plasma levels of carbamazepine, and between plasma levels and clinical efficacy or tolerability are rather tenuous, ⁶ carbamazepine concentrations are occasionally monitored ¹. It is important to remember that carbamazepine induces its own metabolism, so levels taken before 4 weeks may not reflect steady state. ³ The steady-state plasma concentrations of carbamazepine considered as ‘therapeutic range’ vary considerably interindividually: for the majority of patients a range between 17 to 50 micromol/L has been reported. Concentrations of carbamazepine-10,11-epoxide (pharmacologically active metabolite) are about 30% of carbamazepine levels. ⁶

**Phenytoin**
Phenytoin monitoring remains useful because its non-linear kinetics make dose adjustment difficult. ¹ Phenytoin plasma concentrations of 10 to 20mg/L are generally accepted as therapeutic. Plasma concentrations between 5 to 10mg/L can be therapeutic for some patients, but concentrations less than 5mg/L are not
likely to be effective. In most patients maintained at steady dosage, stable phenytoin serum levels are achieved. There may be wide interpatient variability in phenytoin serum levels with equivalent dosages. Patients with unusually low levels may be noncompliant or hypermetabolisers of phenytoin. Care is required in patients with low albumin or renal failure because the consequent reduction in plasma protein binding can lead to misinterpretation of total concentration measurements. Phenytoin plasma concentrations of 10 to 20mg/L correspond to an unbound drug concentration of 1-2 mg/L (fraction unbound, $f_u$ is normally 0.1). If $f_u$ is increased to 0.2, as, for example, in renal disease, the target unbound concentration is still 1-2 mg/L, but the therapeutic range for total drug is 5-10 mg/L.

A number of phenytoin side effects, such as gingival hyperplasia, folate deficiency and peripheral neuropathy do not appear to be directly related to plasma phenytoin concentrations. Conversely, CNS side effects do correlate with plasma concentration.

The newer anticonvulsants have wider therapeutic ranges, so monitoring is rarely performed in practice. Nevertheless, a tentative target range of 3 to 14mg/L has been proposed for lamotrigine, and there is some evidence that adverse effects of lamotrigine may be concentration dependent.

The Diagnostic Medlab recommends the following guidelines for monitoring anti-convulsant therapy:

- monitoring initial stabilisation or change of dose – phenytoin, carbamazepine, phenobarbitone
- suspected toxicity – all drugs
- suspected non-compliance – all drugs
- failure to control seizures – all drugs
- ongoing routine monitoring – phenytoin only, and even this may not be essential.

Anti-cancer drugs

Although chemotherapeutic agents have narrow therapeutic ranges, concentrations are not routinely monitored because of a lack of data on concentration-effect relationships. One exception is methotrexate where folinic acid rescue is based on monitoring the methotrexate concentration 24-48 hours after the high dose therapy and continuing until concentrations are below 0.05µmol/L. 

Psychiatric drugs

Target ranges have been identified for a number of antidepressants and antipsychotics, many of which are subject to genetic polymorphism resulting in
significant differences in dosage requirements eg nortriptyline. The therapeutic ranges for imipramine and amitriptyline are based on the combined concentrations of parent drug and active metabolite (desipramine and nortriptyline respectively). With the exception of clozapine, the routine analyses of drugs used in psychiatry is not common in the UK or NZ, although it is popular in other parts of Europe.

Lithium
Lithium has a narrow therapeutic range and exhibits fairly predictable pharmacokinetic behaviour; it is an excellent candidate for routine therapeutic monitoring. The incidence and severity of acute adverse effects increase significantly with higher plasma concentrations, and there are also a variety of long-term adverse effects that are commonly associated with high plasma concentrations eg fine tremor, weight gain, thyroid abnormalities and cognitive dulling. The target range for acute treatment of mania is 0.8 to 1.2 mmol/L, whereas a range of 0.6 to 0.8 mmol/L is used for maintenance therapy. The ideal time for sampling is just before the dose or at least 12 hours after the previous dose, and steady state levels should be attained within 3 to 5 days. Changes in renal function, fluid and electrolyte balance and interacting drugs can alter drug concentrations as can irregular dosing, poor compliance and missed doses. These factors need to be considered as an explanation for poor therapeutic response or toxicity.

Anti-infectives
Many anti-infective agents have a wide therapeutic range, which means that standard doses can be used. However, with some antibiotics, toxicity is associated with persistently high concentrations or treatment failure with persistently low concentrations.

Aminoglycoside antibiotics
Aminoglycoside antibiotics eg gentamicin display concentration-dependent killing. The aim of treatment is to achieve high peak concentrations but allow the concentration to fall to low levels between doses. For this reason, most hospitals now use once daily dosing of 5 -7 mg/kg and various methods of monitoring levels are implemented.

Glycopeptide antibiotics
Glycopeptide antibiotics eg vancomycin and teicoplanin display time-dependent killing, so the aim is to maintain concentrations above the minimum inhibitory concentration (MIC) for most of the dosage interval. The CCDHB Microbiologists recommend trough concentrations between 10 and 20 mg/L for vancomycin, whereas some hospitals use constant rate infusions aiming to maintain concentrations between 15 and 25mg/L. Teicoplanin concentrations are not measured routinely but can be useful if under dosing is suspected. The data sheet recommends that in patients with impaired renal function, trough
plasma teicoplanin concentrations should be monitored periodically after the first week of therapy and the dosage adjusted to prevent trough concentrations exceeding 30 µg/mL in patients with septic arthritis or 15 µg/mL in other cases, with a minimum of 10 µg/mL. 11

**Anti-fungal drugs**
Amphotericin concentrations are rarely measured. 1 Flucytosine concentrations should be at least 20-25 µg/ml and transiently not more than 100-120 µg/ml. Prolonged concentrations of over 100 µg/ml must be avoided because of the increased risk of side effects. 12 There is some evidence that trough concentrations of itraconazole above 0.5mg/L are desirable so monitoring of this drug could become more common. 1

**Anti-retroviral drugs**
Unexplained treatment failures and a high incidence of drug interactions have led to an interest in the monitoring of anti-retroviral drug concentrations. The protease inhibitors have received particular attention because of their complex and variable pharmacokinetics and the recognised association between trough plasma concentrations and therapeutic response. 1

**Digoxin**

Digoxin has a large volume of distribution, and absorption and distribution of drug takes a long time. For this reason, samples taken less than 6 hours after an oral dose cannot be accurately interpreted as the plasma concentration will be erroneously high. 5 Another common error with digoxin is to ignore the effect of decreased renal function in patients on long-term therapy. As the major route of digoxin elimination is renal excretion of the unchanged medicine, 13 renal impairment can lead to accumulation of drug and have toxic consequences. Although there is considerable variation between patients, plasma digoxin concentrations of 1 to 2nmol/L are generally considered to be within the therapeutic range. 4 Digoxin toxicity is more commonly associated with serum digoxin concentration greater than 2nmol/L; however, toxicity may occur with lower digoxin serum concentrations. In deciding whether a patient's symptoms are due to digoxin, the clinical state together with the serum potassium level and thyroid function are important factors. 13

**Theophylline**

Theophylline is principally cleared by hepatic metabolism, therefore dosage requirements vary widely and drug interactions remain a major concern. 1 The half life of theophylline is increased and clearance decreased in the elderly and in patients with congestive heart failure, chronic obstructive pulmonary disease, cor pulmonale or liver disease. The clearance in premature infants and neonates is also reduced, whereas the serum half life is decreased and clearance increased
in cigarette or marijuana smokers. Bronchodilator effects have been demonstrated within the normal target range of 10 to 20 mg/L but lower concentrations are associated with anti-inflammatory and steroid sparing effects. Consequently, there is some support for reducing the target range to 5 to 15 mg/L which may reduce the incidence of toxic effects. Theophylline in neonates (but not in adults) is converted to caffeine, so the therapeutic range for theophylline in neonatal apnoea is lower: 6 to 12 mg/L (allowing for the contribution of caffeine). The average theophylline half-life is approximately 8 hours; therefore routine monitoring of plasma concentrations can usually begin approximately 24 hours after the initiation of therapy or change in dose. In patients receiving nonsustained-release or liquid dosage forms, monitoring is most reliable when trough levels are obtained. In patients receiving sustained-release theophylline, the time of sampling is less critical. Trough concentrations are recommended, but samples taken at the midpoint of the dosing interval may also be acceptable.

### Commonly monitored drugs

<table>
<thead>
<tr>
<th>Medicine (Therapeutic range)</th>
<th>Elimination $t_{1/2}$</th>
<th>Approximate time to $C_{ss}$</th>
<th>Recommended sampling time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine (17-50 µg/ml/L)</td>
<td>12-17 hours (adult; chronic therapy)</td>
<td>2-4 days (adult)</td>
<td>Trough</td>
</tr>
<tr>
<td>Cyclosporin (150-350 ng/ml)</td>
<td>6-24 hours</td>
<td>5 days</td>
<td>Trough</td>
</tr>
<tr>
<td>Digoxin (1-2 nmol/L)</td>
<td>38 hours (longer if renally impaired)</td>
<td>7 days (longer if renally impaired unless loading dose given)</td>
<td>Trough or &gt;6 hours after oral dose</td>
</tr>
<tr>
<td>Lithium (0.8-1.2 mmol/L acute)(0.6-0.8 mmol/L maintenance)</td>
<td>18-24 hours</td>
<td>5 days</td>
<td>Trough or &gt;12 hours after dose</td>
</tr>
<tr>
<td>Phenytoin (10-20 mg/L)</td>
<td>Dose dependent; usually 20-30 hours</td>
<td>5 days</td>
<td>Trough</td>
</tr>
<tr>
<td>Tacrolimus (5-20 mg/L)</td>
<td>8-12 hours</td>
<td>24-36 hours</td>
<td>Trough</td>
</tr>
<tr>
<td>Theophylline (5-20 mg/L)</td>
<td>6-9 hours (highly variable)</td>
<td>2 days</td>
<td>Trough</td>
</tr>
</tbody>
</table>
CASE STUDIES

Case One

Mrs MS is a 91 year old lady with a history of atrial fibrillation for which she is prescribed digoxin 125mcg daily. She is referred to hospital by her GP as her AF is poorly controlled. Whilst in hospital a digoxin level is reported back as 0.7nmol/L. The medical team decide to increase her daily digoxin dose to 187.5mcg and she is then discharged. One week later Mrs MS has symptoms of nausea, fatigue and blurred vision. She is taken to the Emergency Department by her daughter and another digoxin level is taken. This level is reported back as 3.1nmol/ml and her serum potassium is 3.2mmol/L. Mrs MS’s digoxin is withheld and she is prescribed potassium chloride 600mg SR BD.

Discussion

Mrs MS’s initial digoxin level of 0.7nmol/L was less than the therapeutic range of 1-2nmol/L. Although some patients may achieve symptom control with levels lower than 1nmol/L, Mrs MS’s AF was poorly controlled. It is important to consider non-compliance when a low level is reported and the patient is symptomatic. In this case, non-compliance is not considered by the medical team and her daily dose is increased by 50%. She may well have been taking less than the 125mcg/day prescribed dose. The dose increase results in symptoms of digoxin toxicity, confirmed with a level that exceeds the recommended therapeutic range (3.1nmol/L).

There are several factors that need to be considered when monitoring digoxin plasma concentrations. Mrs MS is elderly and is likely to be renally impaired. As digoxin is predominantly renally excreted, the half life can be significantly increased in patients with renal insufficiency. Digoxin volume of distribution (Vd) is also decreased in patients with renal impairment.

The timing of blood sampling with digoxin is very important in achieving accurate levels. Digoxin distribution follows a two-compartment model. Digoxin first distributes into a small initial volume and then distributes into a larger and more slowly equilibrating tissue compartment. Serum concentrations obtained before complete distribution are commonly high and misleading. It is recommended that levels are taken at least 6 hours after an oral dose, where equilibration is complete. With Mrs MS it is uncertain whether the level was taken greater than 6 hours after her dose, and it is also quite likely that she hadn’t reached steady
state concentration. However, she is displaying symptoms of toxicity and this should be the deciding factor ie it is important to treat the patient not the level.

Where toxicity is suspected, digoxin administration should cease until the serum level has been measured. The long half-life means the decline to sub-therapeutic levels is slow but it is wise to correct Mrs MS’s serum potassium, as hypokalaemia enhances the effect of digoxin. Hypokalaemia can be corrected with potassium supplements either orally or intravenously, depending on the urgency of the situation. In cases where a large amount of digoxin has been ingested hyperkalaemia may be present due to release of potassium from skeletal muscle. Before administering potassium in digoxin overdose the serum potassium level must be known.

High calcium concentrations can also potentiate digoxin toxicity, as well as hypothyroidism (which decreases digoxin Vd).

Finally, there are several drugs that interact with digoxin which in turn affects digoxin concentration. The time course for the expected change in digoxin concentration will depend on whether the drug interaction alters digoxin volume of distribution or clearance or both. Amiodarone is probably the most significant and common drug that interacts with digoxin. Verapamil has modest effects on digoxin clearance and St John’s wort also reduces digoxin concentrations by about 25%. Due to the narrow therapeutic window of digoxin, it is important to consider potential drug interactions. Ideally digoxin levels should be monitored when known interacting drugs are initiated or stopped.

**Case Two**

Mr AB is a 47 year old Polynesian man with end stage renal failure secondary to Type 2 diabetes. He also has a history of hypertension and gout.

He is admitted to hospital at short notice to receive a cadaveric renal transplant. Post transplant he is initiated on triple therapy immunosuppression to prevent allograft rejection:
- Tacrolimus 5mg 12 hourly
- Mycophenolate 750mg 12 hourly
- Prednisone 20mg mane

Mr AB is recovering well from the operation and his serum creatinine has reduced substantially. After receiving his second dose of tacrolimus a blood test is taken to monitor his serum concentration. The level comes back at 20.2mg/L (target range 10-15mg/L) and the Renal Physician decides to omit the next dose and to reduce subsequent doses to 4mg.
Mr AB’s serum concentrations are initially monitored 3 times weekly. When he is discharged 10 days post-transplant, his level is consistent and within the target range of 10 to 15 mg/L. The frequency of his tacrolimus level monitoring decreases to weekly then monthly as his condition becomes more stable. Six months later on a visit to the GP, his previously well-controlled blood pressure is 170/100mmHg and he is prescribed diltiazem 180mg LA daily. He presents to his Renal Clinic appointment 1 week later with headaches and tremors. His serum creatinine is found to be 155µmol/L (baseline 120µmol/L) and his tacrolimus level is 25mg/L.

Discussion

It is important that Mr AB’s tacrolimus blood concentrations stay within the target range in order to suppress graft rejection. Tacrolimus has a narrow therapeutic window, therefore monitoring also minimises the risk of dose-related toxicity.

Mr AB’s initial blood concentration is higher than the target range, and the immediate assumption is that his tacrolimus dose is too high. However, there are important factors that need to be considered when interpreting blood concentrations in relation to a target range. Firstly, it is important that the drug has reached steady state - approximately 3 to 5 half lives. Tacrolimus has a half-life of about 8 to 12 hours (but this can be prolonged if the patient has hepatic impairment), so it is reasonable to wait 24 to 36 hours after initiating or altering therapy before checking tacrolimus blood levels. Mr AB’s blood test was taken after his second dose of tacrolimus so he is unlikely to have reached steady state concentration.

Another important consideration is the timing of the blood sample in relation to the dose. Most target ranges are indicative of blood concentrations taken just before the dose ie a trough level. Mr AB’s initial blood test was taken after his second dose therefore the level can not be accurately interpreted. The Renal Physician is unaware of the errors in blood sample timing and reduces Mr AB’s dose in response to the high level. Mr AB could now potentially be receiving a subtherapeutic dose.

Mr AB is displaying symptoms of tacrolimus-related neurotoxicity at his Renal Clinic appointment. This is confirmed by his high tacrolimus blood level which is also causing nephrotoxicity. Tacrolimus is a substrate for CYP3A4 and P-glycoprotein, and is susceptible to drug interactions with inhibitors or inducers of CYP3A4 or P-GP. Mr AB’s Physician will need to determine whether he was taking any medications or foods that may have interacted with the tacrolimus. Diltiazem is an inhibitor of CYP3A4 and P-GP, therefore when taken concomitantly with tacrolimus, can increase blood levels. Diltiazem is actually frequently prescribed when tacrolimus is initiated to “boost” tacrolimus levels, which allows reduced tacrolimus doses. When used in this manner, its antihypertensive properties are also useful for preventing hypertension.
associated with tacrolimus therapy. Mr AB’s physician could manage this situation by either discontinuing the diltiazem and choosing another antihypertensive that does not interact with tacrolimus, or by decreasing the dose of tacrolimus.

Tacrolimus has a low oral bioavailability and food decreases the rate and extent of absorption. To minimise variability in absorption and therefore the blood levels, tacrolimus should be taken consistently with or without food.

References

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8) Guide to therapeutic drug monitoring. NHS Regional Laboratory for Toxicology, Birmingham. Available from http://www.toxlab.co.uk/tdm.htm#The%20TDM%20Guidelines