Therapeutic drug monitoring

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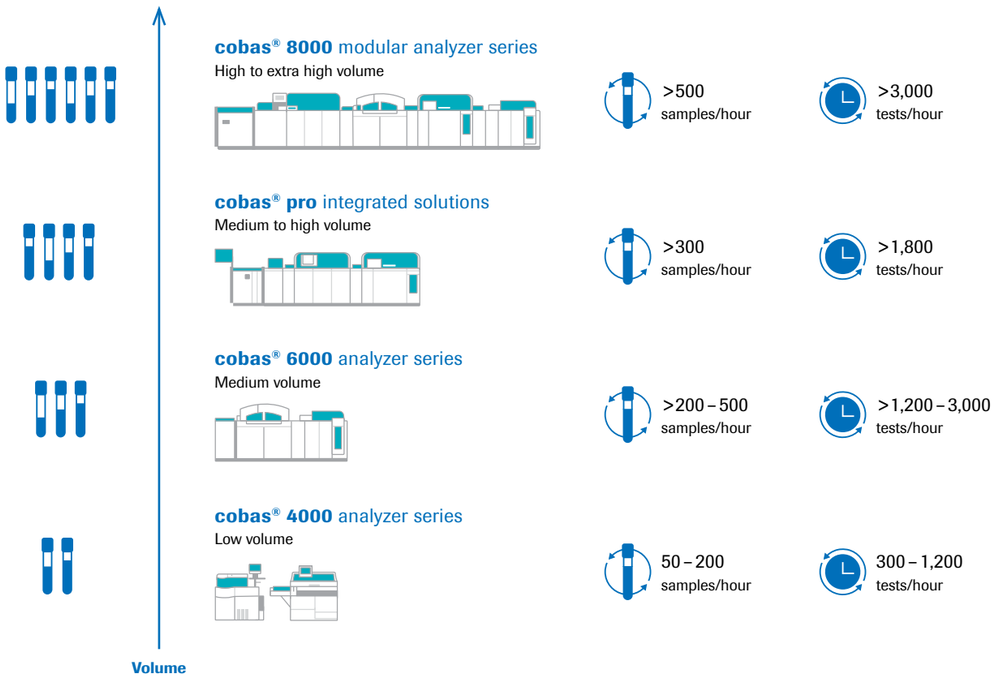

Introduction to therapeutic drug monitoring (TDM)

Clinical benefits of TDM: supporting better patient care through effective and safe drug therapy

The majority of therapeutic drugs have a wide therapeutic range (i.e. there is a large difference between the effective and toxic concentrations) and target concentrations can be achieved using a fixed-dose regimen. However, some have a narrow therapeutic range. This results in a fine balance between maintaining a therapeutically effective concentration, and avoiding toxicity (or side effects) due to overdosing or ineffective treatment due to underdosing.[1]

In addition, a small number of drugs show high inter-person variation in the pharmacokinetic profile. This means that each individual metabolizes, absorbs and excretes the drug at a different rate and the profile can be affected by parameters such as age, genetics, comorbidities, and concomitant medications. For these therapies, the serum or plasma concentration is more closely related to the drug's therapeutic effect (or toxicity) than the dosage. Hence, actual serum (or plasma) concentrations should be measured for the duration of therapy (and often for the remainder of the patient's life) and used to adjust the dosing regimen accordingly. Optimal therapeutic efficacy can, therefore, be achieved for each individual patient through dose adjustment and routine monitoring.[1]

The goal of TDM – to use drug concentrations to achieve therapeutic efficacy for each individual patient[1]

Criteria for establishing TDM have been developed and are shown in Table 1.

• Drugs with a narrow therapeutic range
• Drugs with an unpredictable relationship between dose and plasma concentration
• Drugs for conditions where it is difficult to determine efficacy by clinical methods
• Monitoring of compliance in patients with an apparent non-response to therapy

Table 1: Criteria for TDM[1]

TDM: from therapeutic drug monitoring towards therapeutic drug management

Result interpretation is an integral part of drug monitoring and shifts the emphasis from measuring to monitoring. The test result is frequently used to adjust the dose of therapy to optimize treatment on an individual basis, resulting in a personalized healthcare approach.[1] With the aim of achieving therapeutic efficacy for each individual patient, in addition to measuring the actual concentration of the drug, there are several other factors to consider when interpreting the result, as shown in Table 2.

• Drug administration route and dosing regimen
• Age of the patient
• Health status, including function of the liv er and kidneys (which affect rate of drug metabolism/ elimination)
• Interaction with co-medication
• Protein binding
• Sampling time in relation to last dose
• Pharmacogenomics

Table 2: Additional factors for consideration in TDM[1]

For these reasons the term TDM, which traditionally has applied to the measurement or, at best, monitoring of a drug's concentration, is becoming obsolete. A more appropriate term gaining more widespread use is 'therapeutic drug management' which encompasses the additional factors necessary to achieve the best clinical outcome.[2]

Therapeutic drug management is a combining therapeutic drug measurement, pharmacokinetics, and pharmacogenomics to determine the optimal therapeutic drug dosage and achieve better patient outcomes[1,2]

Developments in TDM

Therapeutic drug monitoring was established in the 1960s[3]. The drugs that require monitoring generally fall into seven categories and those that can be monitored using the Roche TDM portfolio are shown in Figure 3. As can be seen from the figure, some drugs fall into more than one category as they have been licensed for multiple indications.

A short introduction to anti-arrhythmic drug monitoring

Anti-arrhythmic drugs are prescribed to regulate either heart rhythm or heart rate in patients with arrhythmia. Atrial fibrillation is the most common cardiac arrhythmic disorder. It is an indicator of underlying cardiovascular conditions (such as hypertension, coronary and valvular heart disease, and heart failure) and affects approximately 20 million people.[4] Lidocaine, N-acetylprocainamide, procainamide and quinidine are considered to be Class I anti-arrhythmic agents as they block the fast sodium current and require regular monitoring. Digoxin is a frequently prescribed cardiac glycoside and was one of the first drugs to be monitored in patients with heart failure or certain arrhythmias. Along with digitoxin, digoxin is monitored to prevent digitalis toxicity,[5] the warning signs of which include gastrointestinal disorders, neuropsychological disorders and bradycardia.[6] An overview of the target therapeutic ranges is shown in Table 3.

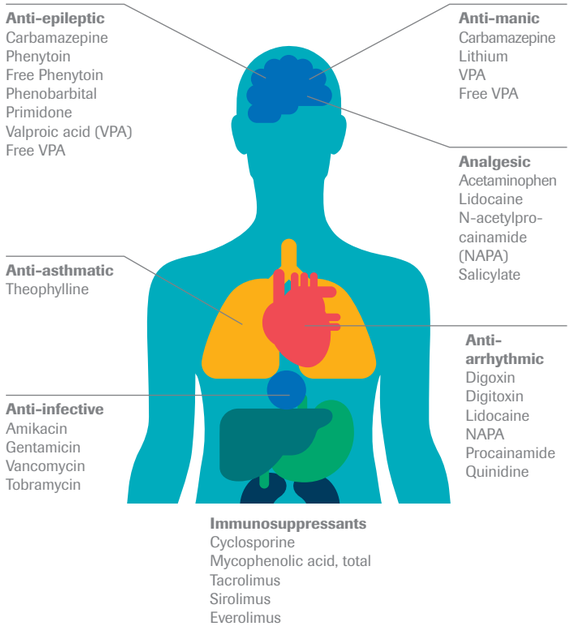

Figure 3: Drugs that can be monitored using the Roche TDM portfolio

Anti-arrhythmic agents	Target therapeutic range
Digoxin	0.5 – 2.0 ng/mL
Digitoxin	15 – 25 ng/mL
Lidocaine	2 – 6 µg/mL
N-acetylprocainamide	15 – 25 µg/mL
Procainamide	4 – 12 µg/mL
Quinidine	3 – 8 µg/mL

Table 3: Overview of therapeutic ranges* for anti-epileptic agents[5,7,8]
*Disclaimer: The target therapeutic ranges given here are a general guide and exact ranges may differ according to therapeutic indication.

Much of the recent TDM literature focuses on digoxin as this is the most frequently monitored drug in this class. One of the reasons for this is that co-administration of several other therapies can result in digoxin toxicity. These include the co-administration of amiodarone, drugs that induce hypercalcemia or hypokalemia, heart-rate lowering drugs, those that prolong the QT interval and drugs that slow cardiac conduction. In contrast, agents, such as sucralfate, acarbose, cytotoxic agents, and enzyme inducers, can reduce plasma concentrations of digoxin.[6] As a result, safety monitoring for digoxin should be undertaken in the following situations: a change in dose of digoxin; a change in dose of concomitant therapy; a change in the patient's clinical state. Samples for monitoring should be taken at least 8 – 10 hours after the last digoxin dose and 8 – 10 days after a dose change. In addition, serum potassium and renal function (as adverse events are potentiated by renal impairment) should be measured periodically.[9]

Co-administration of several other cardiac therapies can result in digoxin toxicity[6]

Another challenge in the therapeutic drug monitoring of digoxin is that immunoassays for digoxin monitoring can be affected by interference from endogenous (digoxin-like immunoreactive substances) and exogenous compounds. Such compounds include: spironolactone, potassium canrenoate,[10] Digibind®, Chan Su, Lu-Shen Wan, oleander-containing herbal preparations, Asian and Siberian ginseng, and Ashwagandha.[11,12] Such assays therefore need to accurately and sensitively measure the drug concentration and not be influenced by other agents.

A short introduction to anti-epileptic drug monitoring

Epilepsy affects around 50 million people worldwide[13] and the goal of treatment is to prevent seizures. However, it can be difficult to monitor treatment response and adverse events by clinical observation alone. This is partly because seizures occur at irregular intervals, and also because side effects can be subtle and difficult to distinguish from the underlying cause.[14,15] In addition, many patients take more than one therapy and an individualized choice of drugs and doses is required to maintain seizure control. For these reasons, monitoring of some anti-epileptic drugs is warranted.[15] An overview of target therapeutic ranges for currently monitored therapies is shown in Table 4.

Anti-epileptic agents	Target therapeutic range
Carbamazepine	4 – 12 mg/L
Phenytoin	10 – 20 mg/L
Phenobarbital	10 – 40 mg/L
Primidone	5 – 10 mg/L
Valproic acid	50 – 100 mg/L

Table 4: Overview of the therapeutic ranges* for anti-epileptic agents[15]
* Disclaimer: The target therapeutic ranges given here are a general guide and exact ranges may differ according to therapeutic indication.

Therapeutic drug monitoring was initially established for phenytoin and has since been introduced for other anti-epileptic therapies. With the older therapies there is wide inter-individual variation in the serum concentration of anti-epileptic drugs. This is due to differences in pharmacokinetics and potentially leads to a wide variation in drug response. Furthermore, drug interaction and non-compliance can affect therapeutic outcome.[14,15] In recent years, several new anti-epileptic therapies (such as gabapentin, lamotrigine, oxcarbazepine, tiagabine, topiramate, vigabatrin and zonisamide) have been developed and approved. This has resulted in more patients taking polytherapy. The newer drugs tend to have a lower potential for interaction, more predictable pharmacokinetic profile, and large therapeutic range. Expert reviews suggest that monitoring of the newer therapies may be helpful but, at present, is not recommended.[16–18] More data are needed and some of the recent literature describes potential for monitoring the newer anti-epileptic therapies.

There is wide inter-individual variation in the serum concentration of the older epileptic drugs due to pharmacokinetic differences potentially leading to a wide variation in drug response[14]

Furthermore, there are special situations, such as during pregnancy, where drug monitoring is particularly useful as listed in Table 5.[14,15]

- To establish an individual therapeutic concentration once a desired clinical outcome has been reached; this can be used to assess potential causes for a change in drug response in the future
- To help diagnose clinical toxicity
- To assess compliance to therapy (especially in the case of uncontrolled or breakthrough seizures)

• To guide dose alterations in patients likely to have increased pharmacokinetic variability (e.g., children, the elderly, patients with comorbidities) or when a pharmacokinetic change is anticipated (e.g., pregnancy, addition or removal of an interacting drug)
• To guide dose adjustments for drugs with dose-dependent pharmacokinetics (e.g., phenytoin)

Table 5: Special situations where monitoring of anti-epileptic drugs is particularly useful[15]

A short introduction to anti-asthmatic drug monitoring

Asthma is the most common chronic disease among children. It affects up to 300 million people worldwide, although asthma is frequently under-diagnosed and under-treated.[19] Theophylline is a bronchodilator that has been used for over 60 years for treating asthma and chronic pulmonary obstructive disease, and it is still widely used today. Due to its narrow therapeutic window, monitoring is essential and should be performed once a pharmacological steady state has been reached. The therapeutic range of theophylline varies due to inter-person variability in pharmacokinetics, but a concentration of 10 – 20 µg/mL is usually optimal. Toxic symptoms are associated with theophylline plasma concentrations higher than 20 µg/mL.[20]

Little has been published in recent years on TDM for asthma. However, more focus may be needed as it has been suggested that over 50 % of patients receiving theophylline are not monitored, especially younger patients.[21] Also, studies of serum concentrations in monitored patients have shown that only about 36 % had levels within the therapeutic range; over 50 % of patients had subtherapeutic levels, and theophylline concentrations were at toxic concentrations in between 2 % and 12 % of patients.[20,22] Such results suggest that many patients are not receiving sufficient treatment and better adherence to therapy and treatment guidelines are needed.

Studies of serum theophylline concentrations in monitored patients have shown that over 50 % had subtherapeutic levels. Theophylline concentrations were at toxic levels in between 2 % and 12 % of patients[20,22]

A short introduction to anti-manic drug monitoring

Anti-manic agents (or mood stabilizers) are used to treat mania and bipolar disorder, which has a lifetime prevalence of 2.4 % worldwide.[23] Lithium and valproic acid are both first-line treatments for acute mania and maintenance treatments for bipolar disorder. Carbamazepine is effective in the treatment of mania.[24] The requirement for effective therapy over a long duration favors the use of monitoring to reduce side effects and optimize treatment. An overview of the target therapeutic ranges for currently monitored therapies is shown in Table 6.

Anti-manic agents	Target therapeutic range
Carbamazepine	4 – 12 mg/L
Lithium	0.8 – 1.1 mmol/L
Valproic acid	50 – 100 mg/L

Table 6: Overview of the therapeutic ranges* for anti-manic agents[15,25,26]
*Disclaimer: The target therapeutic ranges given here are a general guide and exact ranges may differ according to therapeutic indication.

It is common for patients with bipolar disorder to be prescribed more than one therapy. This is in line with treatment guidelines,[27,28] and is another reason why monitoring is important as drug interactions can alter plasma concentrations.[26] An additional requirement for monitoring with anti-manic agents is the possibility of treatment non-compliance, which has been reported to be as high as 64 % in patients with bipolar disorder.[29]

Much of the recent literature has focused on the efficacy of anti-epileptic drugs for the treatment of bipolar disorder and also on the development of newer therapies.[30]

Polypharmacy is common in patients with bipolar disorder[28] *and monitoring is important as drug-drug interactions can alter plasma concentrations.*[26] *Poor treatment compliance is also common in this patient population*[29]

An overview of anti-infective drug monitoring

Many anti-infective agents that are routinely used have a wide therapeutic range and do not need monitoring. However, a few have a narrow therapeutic range and irreversible damage can occur with toxic levels. The most common side effects seen with anti-infective agents that require monitoring are nephrotoxicity or ototoxicity. An overview of the target therapeutic ranges is shown in Table 7. For vancomycin the trough concentration is the most accurate determinant of efficacy and toxicity prevention.[31]

Anti-infective agents	Target therapeutic range
Amikacin	Peak: 25 – 35 µg/mL Trough: 4 – 8 µg/mL
Gentamicin	Peak: 4 – 10 µg/mL Trough: 0.5 – 2 µg/mL
Vancomycin	Trough: 15 – 20 mg/L (Trough: 25 – 40 mg/L for continuous infusion)
Tobramycin	Peak: 4 – 10 µg/mL Trough: 0.5 – 2 µg/mL

Table 7: Overview of the therapeutic ranges* for anti-infective agents[31–33]
*Disclaimer: The target therapeutic ranges given here are a general guide and exact ranges may differ according to therapeutic indication.

Despite monitoring, toxicity can still be a problem as, for example, nephrotoxicity occurs in 10 – 25 % of gentamicin therapeutic courses.[34] Hence, these therapies are generally used to treat more severe or multidrug resistant infections, which are a much reported health problem. However, it has also been shown that use of vancomycin doses close to the minimum inhibitory concentration can induce resistance[35] and a trough concentration of >10 mg/L is recommended.[31] A second role for drug monitoring, therefore, is to prevent resistance by ensuring that patients receive an adequate therapeutic dose.[33]

Some anti-infective agents have a narrow therapeutic range and irreversible nephrotoxicity or ototoxicity can occur.[34] *Drug monitoring is also used to prevent resistance by ensuring that patients receive an adequate therapeutic dose*[33]

Some of the literature on anti-infective therapy and drug monitoring published in the last 5 years has focused on critically ill patients, such as those with burns or sepsis. This is because dosages may need to be increased to achieve therapeutic levels as a result of changes in the drug's pharmacokinetic profile. In patients with burns, lower plasma concentrations of amikacin, vancomycin, gentamicin and tobramycin have been found. These lower concentrations are linked to various factors, including area of the burn, drug clearance, and creatinine clearance.[36–38] Similarly, increased doses of amikacin are needed in critically ill septic patients to achieve therapeutic levels due to an increased volume of distribution.[39] Studies in intensive care units (ICU) have also identified that many of their patients may receive subtherapeutic doses of vancomycin, gentamicin and tobramycin. This is due to changes in drug clearance and underestimated increases in volume distribution.[40,41] In these situations, monitoring is necessary to ensure patients achieve the required therapeutic level.

A short introduction to immunosuppressant monitoring

Immunosuppressants, such as cyclosporine and mycophenolic acid, are used routinely in transplant patients to prevent rejection. Immunosuppressant therapy is a fine balance between transplant rejection caused by subtherapeutic range and infections caused by supratherapeutic ranges.[42]

Additionally, creatinine clearance is used to adjust doses as kidney function often slowly deteriorates over time as a results of cyclosporine toxicity.[42]

The combination of TDM and dose adjustment based on creatinine clearance is one of the first true PHC stories.

Rejection is the main cause of transplant failure in the first year post-surgery. However, many dose adjustments are needed to obtain the required target level in the months following transplantation, as shown in the overview given in Table 8.[42-47]

Immunosuppressant therapies can have severe side effects (including liver or renal failure) which can lead to non-compliance. Also, it is rare that patients are treated with a single drug so the complication of drug–drug interactions becomes an issue, particularly when cyclosporine and mycophenolic acid are used in combination. The rationale for monitoring, therefore, comprises the need to prevent rejection (efficacy and compliance), and avoid side effects.[44] The development of a different cyclosporine formulation has overcome some of the variability issues, but significant inter- and intra-individual variability still occurs in the phase between administration and maximum concentration.[42] Similarly, there is wide inter- and intra-variability in the pharmacokinetics of mycophenolic acid. Use of the recommended standard dose of mycophenolic acid (0.5 – 1.0 g twice daily) can result in over- or under-immunosuppression.[48] However, despite a link between rejection and mycophenolic acid plasma concentration,[49] the use of monitoring is controversial.[50]

Anti-inflammatory agents	Target therapeutic range
Cyclosporine	Renal transplant patients (C2 level): By Day 5, >1,700 ng/mL; in Month 1, 1,600 – 2,000 ng/mL; Month 2, 1,400 – 1,600 ng/mL; Month 3, 1,200 – 1,400 ng/mL; Months 4 – 6, 800 – 1,000 ng/mL; Months 7 – 12, 600 – 800 ng/mL; Month 12 onwards, ~800 ng/mL (assuming no induction, mTOR inhibitor or IL-2 receptor antibody therapy) Liver transplant patients (C2 level): Months 0 – 3, 1,000 ng/mL; Months 4 – 6, 800 ng/mL; Month 7 onwards, 600 ng/mL
Mycophenolic acid	Renal: AUC 30 – 60 mg•h/L Liver, bowel, pancreas: trough 1.0 – 3.5 mg/L (for monotherapy) Cardiac: trough >2 – 3 mg/L (in combination with tacrolimus)
Tacrolimus	Renal transplant patients (C0 level): 0 to 3 months, 10 – 15 ng/mL; >3 to 12 months, 5 – 15 ng/mL; >12 months, 5 – 10 ng/mL (assuming no induction, mTOR inhibitor or IL-2 receptor antibody therapy)
Sirolimus	C0 5 – 15 µg/L
Everolimus	C 3 – 8 ng/mL

Table 8: Overview of the therapeutic ranges for immunosuppressants[42-47]

*Disclaimer: The target therapeutic ranges given here are a general guide and exact ranges may differ according to therapeutic indication.

The main advance in monitoring of cyclosporine and mycophenolic acid is the evolution of the measuring parameter. The 12-hour area under the plasma concentration-time curve was initially used to measure exposure to cyclosporine and is the best measure of exposure to mycophenolic acid. However, it is not clinically practical to draw samples over this time period. Measuring the trough level was considered for both therapies as it is simpler. However, for cyclopsorine a poor correlation of trough measures with rejection and area under the curve (AUC) over 12 hours was found. In addition, trough levels as a measure of mycophenolic acid is not accurate due to intra-patient variability.[42]

Subsequently, investigations of cyclosporine monitoring found that the AUC over the first 4 hours following administration correlates well with the AUC over 12 hours, and required fewer blood draws. More recently, the C2 level (concentration 2 hours after administration) has become the recommended measure for assessing exposure to cyclosporine in transplant patients. The C2 level correlates well with the AUC over 4 hours.[42,51] Samples should be taken at 2 hours post-dose ±15 minutes.

For mycophenolic acid monitoring, many studies have investigated limited sampling methods and associated algorithms to determine the AUC and have provided accurate estimates. Co-medication should be considered when selecting the algorithm, however.[49,52] One such study found sampling blood at 0- (pre-dose), 0.66- and 2 hours after administration of mycophenolate mofetil showed the best predictive performance.[48]

The rationale for monitoring immunosuppressant drugs comprises the need to prevent rejection (efficacy and compliance), and avoid side effects and infections[44]

Analgesic drugs

Some analgesics, such as acetaminophen and salicylate, are available over the counter and are widely used for pain relief.[53] For these and other analgesic agents, monitoring is mainly used if overdose (accidental or deliberate), toxicity or abuse are suspected. An overview of the target ranges is shown in Table 9.

Analgesic agent	Target therapeutic range
Acetaminophen	10 – 20 mg/L
Lidocaine	2 – 6 µg/mL
NAPA	15 – 25 µg/mL
Salicylate	100 – 250 mg/L

Table 9: Overview of the therapeutic ranges* for analgesic agents[9,53]

*Disclaimer: The target therapeutic ranges given here are a general guide and exact ranges may differ according to therapeutic indication.

Careful monitoring and adjustments to the dose and dosing interval also play a particular role in managing pain control in patients with reduced renal (or liver) function, especially with opioid-based analgesics. This is due to the occurrence of adverse effects and the potential for overdosing.[54]

Guidelines for the management of chronic pain suggest that before patients receive long-term pharmacological treatment a mechanism is put in place to monitor side effects and compliance.[55] Similarly, for conditions such as lower back pain, monitoring for both safety and efficacy is suggested with long-term use and drug therapy should be part of a comprehensive pain care management approach, including rehabilitation.[56]

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